Autologous Fat Grafting and Injectable Dermal Fillers for Human Immunodeficiency Virus–Associated Facial Lipodystrophy: A Comparison of Safety, Efficacy, and Long-Term Treatment Outcomes

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Background: Facial lipoatrophy is a common side effect of human immunodeficiency virus treatment with highly active antiretroviral therapy. To identify the most clinically durable and efficient way of addressing facial lipoatrophy, the authors reviewed all available evidence for the use of injectable dermal fillers and autologous fat transfers as treatment modalities, focusing on safety, outcomes, and long-term durability.

Methods: A systematic review of the Cochrane and MEDLINE databases for autologous fat transfer and injectable dermal fillers for the treatment of human immunodeficiency virus–associated lipodystrophy was performed. Based on U.S. Food and Drug Administration approval in human immunodeficiency virus lipoatrophy, studies were limited to the use of hyaluronic acid and/or poly-L-lactic acid. Facial volume, subjective patient satisfaction, standardized outcome scales, reinjection rates, and complications were recorded.

Results: Nineteen studies were included representing 724 patients, with 549 patients in the hyaluronic acid/poly-L-lactic acid cohort and 175 in the autologous fat transfer cohort. Improvements in facial volume and durability of treatment were similar between dermal fillers and fat transfer, as measured by both objective means and subjective patient outcomes. However, poly-L-lactic acid was reinjected at a rate three times that of autologous fat, and was associated with a relatively high rate of subcutaneous papule formation at 22 percent (range, 3 to 44 percent).

Conclusions: Dermal fillers and autologous fat transfer are effective treatment modalities for human immunodeficiency virus–associated facial lipoatrophy, with high rates of facial volume restoration and patient satisfaction. Autologous fat transfer may offer similar to superior long-term durability but with less of a financial burden compared with injectable fillers. (*Plast. Reconstr. Surg.* 131: 499, 2013.)

The prevalence of lipoatrophy in patients receiving highly active antiretroviral therapy for human immunodeficiency virus ranges between 3 and 35 percent in the literature. Although this range may be accounted for by differences in patient demographics such as duration of therapy and body habitus, the negative impact of facial lipodystrophy toward quality of life has been well documented.[1–4] Multiple studies have shown the psychological effects of facial lipoatrophy with high reported rates of depression, anxiety, distress, and social isolation directly resulting from living with these acquired defects.[5–9] For pa-

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tients with human immunodeficiency virus/acquired immunodeficiency syndrome, the burden of social nontolerance in interpersonal relationships and the workplace is only further exacerbated by outward manifestations of the disease, and the reported noncompliance or nonadherence to treatment regimens as a result of these side effects.[10]

Facial lipoatrophy is characterized by region-specific adipocyte atrophy and hypertrophy and is therefore also referred to broadly as human immunodeficiency virus–associated lipodystrophy syndrome. Specifically, patients experience lipoatrophy in the face and extremities, separate from the generalized wasting of chronic disease also commonly seen in human immunodeficiency virus/acquired immunodeficiency syndrome, or in comparison with the lipohypertrophy of the cervicodorsal region ("buffalo hump"), breasts, and lower abdomen.

Given the continued prevalence of human immunodeficiency virus and facial lipoatrophy, an increasing number of patients require correction of these facial manifestations. Currently, treatment interventions include injectable dermal fillers, with poly-L-lactic acid as the only U.S. Food and Drug Administration–approved filler for treatment of human immunodeficiency virus facial lipoatrophy, and multiple off-label reports of other compounds, including hyaluronic acid. Autologous fat grafting has recently become an increasingly popular technique for both reconstructive and cosmetic local soft-tissue augmentation. However, little is known about the fate of fat transferred into a region affected by lipoatrophy, and so the long-term durability of fat grafting in comparison with hyaluronic acid and poly-L-lactic acid fillers in this clinical setting is currently unclear.

We undertook this systematic review to identity all available reports in the literature of autologous fat grafting in the setting of human immunodeficiency virus/highly active antiretroviral therapy associated facial lipoatrophy, for a comparison of durability, safety, and clinical outcomes with hyaluronic acid and poly-L-lactic acid injectable fillers.

PATIENTS AND METHODS

Literature Search

A systematic review of the Cochrane and MEDLINE databases was completed from 1981 to May of 2012 to identify all clinical reports of facial lipoatrophy treated with autologous fat grafting or the injectable fillers hyaluronic acid and poly-L-lactic acid. Exclusion criteria included studies with less than 1 year of clinical follow-up; reported treatment cohorts of less than five patients; nonfacial (buffalo hump) lipoatrophy/lipodystrophy treatments; non-English studies; and injections with permanent materials including silicone, hydroxyapatite, polyacrylamide, methyl methacrylate, and microsphere collagen.

Data Extraction and Statistical Analysis

Reports were reviewed manually for patient demographics, including lipoatrophy severity, clinical follow-up, patient-reported outcomes, injection volume/frequency, tissue augmentation thickness and longevity, and any injection-associated complications. Subjective data were reported directly and compared between groups, and all frequency data were adjusted to provide an average rate per treatment modality, where a value of $p < 0.05$ was considered statistically significant.

RESULTS

Search Results

The initial database query involved two search strings. The first string identified all reports of "autologous fat grafting/dermal fat grafting" and "lipoinjection" for a total of 910 reports. The second search string identified all reports of "hyaluronic acid," "poly-L-lactic acid," and "filler" for a total of 20,720 reports. These search strings were then meshed with the primary query of "lipodystrophy/lipoatrophy/human immunodeficiency virus–associated lipodystrophy syndrome." This strategy identified 26 primary reports for autologous fat grafting and 113 primary reports using injectable fillers, all in the setting of human immunodeficiency virus–associated lipoatrophy. These 139 reports were reviewed manually for relevance, and any additional studies not captured by the initial search were included following bibliographic review.

After application of the exclusion/inclusion criteria, a total of 19 primary studies were included in this review.[11–30] Figure 1 demonstrates the study attrition characteristics of the systematic review. Hyaluronic acid and/or poly-L-lactic acid fillers were used exclusively in 12 studies, and autologous fat transfer was used in seven studies.

Of the studied outcome criteria including objective efficacy as measured by tissue volume before and after filling treatment, subjective and/or patient-reported efficacy, subsequent injection rates, and adverse events, all reports included at least one of these outcomes. No report contained

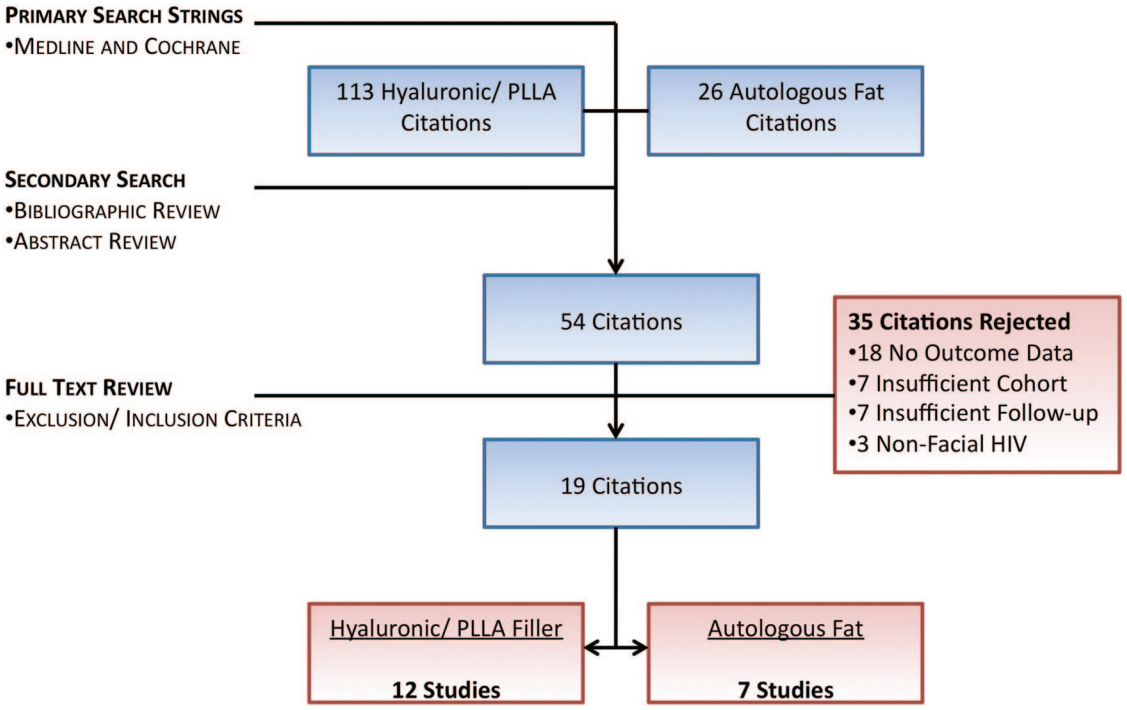

Fig. 1. Study attrition characteristics. *PLLA*, poly-L-lactic acid; *HIV*, human immunodeficiency virus.

all of these outcomes. Because of the variability of the data and interval reports, only a limited comparative statistical analysis without meta-analysis outcomes could be generated, and an adjusted p value was not used.

Study Characteristics

Patient Demographics

In the 19 studies reviewed, a total of 724 patients were represented, with 549 patients in the hyaluronic acid/poly-L-lactic acid groups and 175 patients in the autologous fat transfer group. Among those that received hyaluronic acid/poly-L-lactic acid treatment, patient ages ranged from 30 to 74 years old, human immunodeficiency virus duration ranged from 2 to 24 years, and highly active antiretroviral therapy treatment duration ranged from 3 months to 23 years. This was in comparison with the autologous fat transfer group, where the patient ages ranged from 14 to 70 years, with 7 to 16 years of reported human immunodeficiency virus infection and 3 to 13 years of highly active antiretroviral therapy. Table 1 lists the patient demographics of all included studies.

Tissue Volume

Eight studies reported absolute facial tissue volume after treatment versus volume before treatment, with sustained tissue thickness at 12 months. Six of these studies evaluated hyaluronic acid or poly-L-lactic acid, for a total of 247 patients. Results at 1 year demonstrated statistically significant stability of facial thickness changes following baseline measurements. Lafaurie et al.,[26] Cattelan et al.,[26] and Valantin et al.[29] demonstrated a statistically significant increase in tissue thickness, but a wide range of sustained thickness were noted, ranging from 2.3 to 7.2 mm ($p < 0.001$). In addition, Skeie et al.[11] demonstrated the longest clinical follow-up at 36 months, with a sustained increase of tissue thickness at 6 mm ($p < 0.001$), and in those studies reporting a percentile increase of tissue thickness at follow-up, a range of 60 to 73 percent ($p < 0.001$) was demonstrated.[19,22]

Outcomes were similar in the autologous fat transfer studies, with sustained increases in facial volume persisting at long-term follow-up. Nelson and Stewart[17] found an average increase in tissue thickness of 2.63 mm at 1-year follow-up, and Fontdevila et al.[15] reported an average increase in baseline tissue thickness of 110 percent at 12 months (average increase, 1.72 ml; $p < 0.001$) in 26 patients. Index transfers ranged in volume from 6.53 to 11.46 ml.

However, because of the heterogeneity of the data reported in both groups, a weighted mean tissue thickness improvement could not be calculated. In addition, there was variability in both the volume injected per treatment, and the frequency and criteria for subsequent injections in the initial

Table 1. Reported-Patient and Study Demographics

Study	Intervention	No. of Patients	Men	Age (yr), Mean (Range)	Years With HIV, Mean (Range)	Years of HAART, Mean (Range)
Valantin et al., 2003[29]	PLLA	50	49/50	45.9 (33.1–58.0)	—	8.6 (1.1–14.1)
Burgess et al., 2005[23]	PLLA	61	61/61	45.5 (35–74)	12.9 (2–23)	7.18 (2–17)
Lafaurie et al., 2005[26]	PLLA	94	88/94	44 (30–64)	—	>3 mo
Cattelan et al., 2006[20]	PLLA	50	42/50	41 (35–69)	—	5.6 (1.2–10.9)
Mest et al., 2006[21]	PLLA	99	97/99	45 (32–65)	13.4 (2–24)	9.1 (2–22)
Moyle et al., 2006[22]	PLLA	27	25/27	41	—	—
Denton and Tsaparas, 2007[19]	PLLA	18	18/18	47.2 (37–58)	—	>3 mo
Levy et al., 2008[16]	PLLA	27	27/27	49 (34–65 ± 8.4)	—	—
Mest and Humble, 2009[13]	PLLA	65	63/65	45.9 (34–66)	14.7 (3–23)	10.4 (3–23)
Bugge et al., 2007[18]	HA	20	19/20	49 ± 7	13.6 (6.9–15.6)	10.0 (6.9–15.6)
Bechara et al., 2008[14]	HA	21	21/21	47.2 ± 7.9	11 (8–20)	—
Skeie et al., 2010[11]	HA	17	—	—	—	—
Dollfus et al., 2009[12]	AFT	6	3/6	17 (14–19)	—	10.2 (7–13)
Serra-Renom and Fontdevila, 2004[27]	AFT	38	26/38	28–56	—	—
Strauch et al., 2004[28]	AFT	5	1/5	Mid-40s	>10	>10
Burnouf et al., 2005[24]	AFT	33	27/33	45 (33–70)	13 (7–16)	7 (3–13)
Guaraldi et al., 2005[25]	AFT	41	28/41	43 ± 6	—	5.4 ± 1.4
Fontdevila et al., 2008[15]	AFT	26	18/26	45.07 (34–59)	—	—
Nelson and Stewart, 2008[17]	AFT	26	24/26	—	—	—

HIV, human immunodeficiency virus; HAART, highly active antiretroviral therapy; PLLA, poly-L-lactic acid; HA, hyaluronic acid; AFT, autologous fat transfer.

treatment period among all studies. Criteria for reinjection or volumes at index or subsequent treatment were not reported, thereby possibly limiting the significance of the absolute difference for tissue thickness between different studies.

Patient-Reported Outcomes

Fifteen studies reported subjective efficacy outcomes, where subjective lipodystrophy severity was found to significantly improve, with excellent treatment satisfaction rates following treatment with both dermal fillers and autologous fat transfers. In the 12 dermal filler studies, a total of 513 patients were evaluated. Satisfaction with outcomes was sustained at long-term follow-up, with Skeie et al.[11] reporting a mean increase in Rosenberg Self-Esteem Scale score to 48 ± 8 from 41 ± 10 ($p < 0.05$; maximum score, 100) at baseline and 17 of 19 (89 percent) of patients classifying facial appearance after treatment as "very much improved," "moderately improved," or "somewhat improved" using the Global Aesthetic Improvement Scale at 3-year follow-up. In studies comparing visual analogue scale scores before and after treatment, mean scores were uniformly higher after treatment, with Lafaurie et al.[26] reporting improvement from 3.4 to 6.8 at 12 months ($p < 0.001$) and Moyle et al.[22] reporting an increase from 2.5 to 5.8 (maximum score, 10) at 2-year follow-up.

However, Burgess et al.[23] found that the proportion of patients self-reporting significant improvements in facial appearance decreased with length of follow-up, with 10 of 61 patients reporting significant improvement at 12 months, falling to nine of 61 and five of 61 at 18 and 24 months, respectively.

Among the three autologous fat transfer studies, similar improvement was demonstrated using subjective outcomes data. Dollfus et al.[12] reported 100 percent ($n = 6$ of 6) patient satisfaction at a maximum follow-up of 1.8 years. Twenty-six of 28 patients (93 percent) in the study by Burnouf et al.[24] reported improvement in facial appearance at 12 months, and Serra-Renom et al.[27] reported a mean shape and symmetry score associated with outcome satisfaction of 3.7 of 4 at 12 months.

Subsequent Injection Rates

Rates of repeated or subsequent injections were reported in 12 studies. Overall, patients treated with poly-L-lactic acid received more sets of injections than patients treated with hyaluronic acid or fat transfer.

Eleven dermal filler studies described reinjection beyond the initial treatment. The total number of dermal filler treatments ranged from one to six separate sets of injections. The majority of patients in poly-L-lactic acid studies received three or more treatments. Mest and Humble[13] reported that 96 of 99 patients (97 percent) received three or more treatments, with 43 of 99 (43 percent) receiving up to six sets of treatment. Similarly, 100 percent of the 94 patients in the study by Lafaurie et al.[26] and 61 patients in the study by Burgess et al.[23] received at least three sets of injections. Studies exclusively using hyaluronic acid injections described a maximum of two sets of injections. In

studies using poly-L-lactic acid, the volume of filler injected ranged from 2 to 8 ml per injection, whereas in those studies using hyaluronic acid, 1 to 6 ml was injected.

One autologous fat transfer study reported more than one set of injections. Serra-Renom et al.[27] reported that 12 of 26 (46 percent) patients required a total of two treatments.

Safety

Twelve dermal filler and three autologous fat transfer studies reported safety outcomes or rates of adverse outcomes. The most common complications following dermal filler treatment were pain, bruising, and redness. Among all reported hyaluronic acid and poly-L-lactic acid study complications, 120 of 451 (27 percent) patients reported postinjection bruising, redness, or pain at the site of injection. Lafaurie et al.[26] reported a severe anaphylactoid reaction following poly-L-lactic acid injection in one of 94 patient (1 percent). Total reported subcutaneous papule formation occurred in 22 percent of patients ($n = 65$ of 300), all of whom were treated with poly-L-lactic acid in five studies.[13,22,23,26,29] In these studies, rate of papule formation ranged from two of 61 (3 percent) to 22 of 50 patients (44 percent).

No serious adverse events or papule formations occurred in the cohort of autologous fat transfer studies. None of the studies reported any incidence of pain, bruising or redness following injection. In contrast, Fontdevila et al.[15] described adverse cosmetic outcomes including asymmetry in three of 26 (12 percent) and undercorrection in two of 26 patients (8 percent), whereas Burnouf et al.[24] reported overcorrection in one of 33 patients (3 percent). Uniquely, Guaraldi et al. described progressive facial lipohypertrophy 2 years after treatment in four of 41 patients (10 percent).[25]

DISCUSSION

The clinical presentation of human immunodeficiency virus–associated facial lipodystrophy is based on wasting of the buccal and/or temporal fat pads with prominence of the zygomaticus, levator labii superioris alaeque nasi, and the orbicularis oris and orbicularis oculi. Previously, we characterized the defects as a series of triangles created by the lipodystrophy, resultant skin laxity, and underlying facial muscular prominence. The first and second triangles present as defects above and below the zygomaticus, thereby creating prominence of the interposed nasolabial fold. The third triangle is observed as a hollow superior to the zygomatic arch secondary to temporal fat pad wasting. Finally, a fourth triangle at the angle of the mandible may be observed with more severe manifestations of the disease secondary to cystic degeneration of the parotid glands.[31] Similarly, James et al. and Funk et al. have proposed progressive grading systems, focusing on the severity of presentation in the nasolabial/malar regions or photographic evaluations of disease severity.[31,32]

This review demonstrates the long-term stability of both dermal fillers and autologous fat transfer for human immunodeficiency virus–associated facial lipoatrophy. Patient satisfaction scores and long-term tissue thickness scores were significantly increased from pretreatment baseline values in both groups when measured at 1-year follow-up. There were no adverse outcomes within the autologous fat transfer groups outside of suboptimal aesthetic outcomes such as overcorrection or asymmetry, presumably related to the variability of graft viability and resorption. In contrast, the dermal filler groups demonstrated rates of bruising and pain in 27 percent of patients. These groups also reported complications based on the foreign-body nature of the filler, with nodule or papule formation in 15 percent of patients treated with poly-L-lactic acid, and an anaphylactic reaction following index injection.

Despite this increased rate of complications in comparison with autologous fat grafting, poly-L-lactic acid is the only U.S. Food and Drug Administration–approved injectable treatment to directly affect the changes following human immunodeficiency virus lipodystrophy. This approval was granted in 2004, based on two European open label studies.[22,29] A supportive U.S. study for U.S. Food and Drug Administration approval was provided by Mest and Humble in 2006.[21] The authors concluded that poly-L-lactic acid is a safe and well-tolerated option for human immunodeficiency virus lipodystrophy. Of note, this benchmark study reported a 13 percent rate of papule formation with a wide range of time to presentation. The majority of papule formation occurred within the 3- to 4-month interval, with two occurring in the first month and some occurring as late as at 12-month follow-up. Of these, 54 percent resolved in the following 6-month interval, whereas the remaining persisted for the duration of follow-up. Similar studies have reported papule formation rates ranging from 6 to 52 percent, with most authors reporting some element of papule formation, and higher rates in reported studies where the investigators specifically sought the occurrence of the papules.[16,21,23,29]

The cause of the papule formation remains unclear. Some theorize the micronodules to be a result of aberrant collagen growth and recommend treat-

ment with intralesional injection of corticosteroids and mechanical disruption using small-gauge needles with multiple passes. However, recurrence can be common with any method.[17] Lemperle et al. made the distinction between early micronodule or papule formation as a result of improper intradermal injection from the more ominous complication of granuloma formation unresponsive to steroid injection.[33] The latter seem to be a result of a local inflammatory responsive and often necessitate excision. Of the studies included in this review reporting papule formation, most were noted to be nonvisible and resolved within 6 months to 1 year. These findings seem to indicate that the reported complications of nodule formation were most likely consistent with early micronodule formation, rather than the delayed presentation of persistent inflammatory granulomas. The most prominent factors for papule formation seem to be intradermal injection, cumulative volume of poly-L-lactic acid injection, location of treatment, and ratio of poly-L-lactic acid dilution. The cumulative volume as a relationship to papule formation seems to be related to the natural relationship of larger volumes causing greater areas of collagen formation and therefore papules. Similarly, a dilutional ratio that allows for greater diffusion of the product may also realize a lesser rate of papule formation. Woerle et al. reported a papule rate of 10 percent at a dilution of 3:1, a common ratio for which other authors have noted a range of papule formation ranging from 13 to 45 percent.[21,29,34] With regard to location, the infraorbital area seems to be the most common site of formation. Practitioners should therefore pay particular attention to technique when addressing this region. Overall, the rare incidence of physical complaints related to the nodules may limit their clinical significance, although they should certainly remain a point of physician and patient discussion.

In comparison, grafted fat can exhibit many of the qualities of the ideal filler, with an autologous and biocompatible composition, ability to be naturally integrated into host tissues, and potential to be permanent.[35] After fat harvest, preadipocytes are preferentially transferred both by virtue of their density in fatty tissue, with as many as 5000 adipose-derived stem cells per gram of fat, and their superior durability compared with the fragile, lipid-filled adipocytes.[36] Some of the long-term durability of the grafted fat may be attributable to tissue ingrowth and fibrous tissue replacement from the host environment. In addition, Eto et al. recently demonstrated a dynamic process of adipocyte survival and found that only a small number of adipocytes within a 300-μm margin of normal tissue survived following initial transplantation, with a slowly progressive augmentation of the viable zone as a result of either newly regenerated and/or repaired initially nonviable adipocytes.[37] Complications following autologous fat grafting seemed limited to cosmetic asymmetry, with the exception of Guaraldi et al., who reported progressive lipohypertrophy of the grafted basins in four of 41 patients (10 percent) at 2 years.[25] This complication can be particularly recalcitrant to treatment. The lipohypertrophy also occurred at the dorsocervical harvest site in those four patients but was not reported by other authors.

Finally, a cost analysis between both methods is complicated by market variability and the variation in number of treatments. However, Hornberger et al. examined eight studies reporting their use and financial practices with poly-L-lactic acid injections. Using these reports, a calculated average cost of $3690 per treatment course was found, based on the average number of units injected.[38] Autologous fat transfer is subject to greater variation in cost from surgeon to surgeon; however, based on our experience, a reasonable estimation is $1200 to $1600 in anesthesia and facility fees, in addition to surgeon fees, which would vary on the overall volume injected. Despite the variability and reporting bias associated with both filler and autologous fat injections, if in fact there is a lower average session cost for fat grating, and perhaps a greater need for repeated filler injections, autologous fat grafting certainly appears to be more economically advantageous for the patient.

CONCLUSIONS

This review demonstrates the efficacy, safety, and durability of both dermal fillers and autologous fat transfer for the treatment of human immunodeficiency virus–associated facial lipoatrophy. Limitations in data and heterogeneity in reporting modalities negated any statistically significant comparison. However, although autologous fat grafting is a more invasive procedure, there may be a number of potential advantages. Poly-L-lactic acid is associated with a significant rate of subcutaneous papule formation, whereas there were no reported side effects related to autologous fat transfer other than technique-associated overfilling or underfilling. In addition, it seems evident that treatment with poly-L-lactic acid typically requires multiple reinjections, but autologous fat transfer was efficacious in the ma-

jority of patients with a single treatment. Finally, harvesting may be performed at sites of lipohypertrophy such as the buffalo hump or abdomen, thereby addressing additional cosmetic manifestations of the lipodystrophy syndrome.

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Evidence-Based Medicine: Questions and Answers

Q: What papers are amenable to Level of Evidence grading? What if my paper is not amenable to grading? Will *PRS* consider it for publication?

A: A good rule of thumb is as follows (these papers are not amenable to LOE grading):

- Animal studies
- Cadaver studies
- Basic science studies
- Review articles
- Instructional course lectures
- CME courses
- Editorials
- Correspondence

As far as what is or is not ratable, the standard is to exclude basic science, bench work, animal, and cadaveric studies because the information gained from these studies is not something that can be applied directly to patient treatment decisions.

PRS definitely welcomes such papers, and such papers will be considered for publication. As indicated above, the LOE grade is a number, a quantitative designation for data. Papers that cannot be graded for Level of Evidence grade are not "worse" than those that can be graded.