Biostimulatory Injectables for the Treatment of Cellulite and Gluteal Enhancement

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Received Date: 04 September, 2018; Accepted Date: 28 September, 2018; Published Date: 08 October, 2018

Abstract
The biostimulatory injectable fillers poly-l-lactic acid and calcium hydroxylapatite have numerous indications and are increasingly used by dermatologists for novel applications. Initially approved for the treatment of HIV-associated lipoatrophy, their stimulation of collagen synthesis leads to a filling effect with long-lasting results. As such, they can be used for numerous cosmetic purposes including wrinkles, scars, and body contouring. In this review, we discuss the biological properties and indications for these two fillers, as well as our experience and technique in using them to treat cellulite and in gluteal enhancement.

Introduction
Since the late 1990’s, the biostimulatory injectable fillers Poly-L-Lactic Acid (PLLA) and Calcium Hydroxylapatite (CHA) have been used for cosmetic purposes such as treating wrinkles, improving skin volume, and treating scar lesions [1]. Unlike exogenous collagen, silicone, or fat injections, these fillers induce an immune reaction that leads to the deposition of new collagen fibers with longer lasting results for the patient [2,3]. Both Poly-L-Lactic acid (Sulptra™) and Calcium Hydroxylapatite (Radiesse™) were initially developed and FDA approved for treating HIV-associated lipoatrophy of the face with positive results [3,4]. Soon after their release, many dermatologists began using them off-label for various other cosmetic issues. Recently, both products have been approved by the FDA for the treatment of facial wrinkles and nasolabial fold contour deficiencies [5]. Their efficacy in treating acne and varicella scars, chest wall deformities, stretch marks, and skin laxity in the upper arms, thighs, abdomen, dorsal hand, and neck is also being investigated [6-11]. However, there is a paucity of literature demonstrating the use of either of these injectables for the treatment of cellulite or for gluteal enhancement. The goal of this article is to investigate their properties and their possible effectiveness in managing both of these issues, and to describe a gluteal enhancement procedure that has shown promising results in our patients.

Skin Collagen Properties and the Changes Seen in Aging Skin
To better understand why these injectables have demonstrated success in treating various cosmetic issues, it is necessary to have a basic understanding of collagen’s role in healthy skin and the changes that take place in aging skin. Collagen is important for maintaining the structure and tensile strength of not only the skin but of all connective tissue in the body and is needed for the support of the biomechanical function of these tissues [12]. In the skin, specifically, type I collagen fibrils provide the mechanical stability and attachment sites for fibroblasts, the cells that produce more collagen [13]. The superficial fascia is a collagenous structure which maintains the separation of the two layers of subcutaneous fat. It has been suggested to be involved in the pathogenesis of numerous cosmetic issues, including cellulite [14,15].

Aging skin and wrinkles are the result of a loss of tone and elasticity in the skin over time secondary to a myriad of factors including smoking and sun exposure [6]. Changes in the skin associated with wrinkles include increased skin laxity, gravitational forces on the soft-tissue, loss of both muscle and fat volume, changes in fat distribution, erosion of bony landmarks, slower skin...
cell turnover, and deterioration of the skin quality both intrinsically and extrinsically [10,13,16,17]. Collagen fragmentation is a major histologic feature of aging skin, with significant fragmentation of the collagen occurring in the extracellular network of the dermis. This can lead to a loss of dermal thickness in late adulthood, sometimes up to 20% [18]. Collagen fragmentation not only weakens the dermis but also causes a decrease in fibroblast activity, with lower levels collagen synthesis and an increased rate of collagen breakdown by collagen-degrading enzymes [13]. Accompanying this process is usually concomitant lipoatrophy, a disproportionate loss of subcutaneous fat to overall weight [11,19]. This is especially evident in the face where subcutaneous fat is partitioned into discrete compartments that show signs of aging at different rates leading to the typical facial wrinkles and pronounced nasolabial folds [13]. It is also this loss of subcutaneous fat on the dorsum of the hands that give them a wrinkled appearance [9].

The changes seen in aging skin are very similar to the effects of HIV-associated lipoatrophy, the result of a combination of rapid weight loss and side effects of antiviral medications. It is because of similarities of the physical characteristics of aged skin to HIV-associated lipoatrophy that some dermatologists have started to use both PLLA and CHA as off label treatments for aging skin.

**Poly-L-Lactic Acid**

Poly-L-Lactic Acid, a member of the alpha-hydroxy acid family, has historically been used in medical devices as a component of absorbable sutures and screws [1,16]. It wasn’t until 1999 when injectable PLLA was first introduced as an FDA approved cosmetic volume enhancer for HIV lipoatrophy of the face and, later, for cosmetic indications like nasolabial fold deficiencies and wrinkles [1,5]. In contrast to traditional fillers such as exogenous collagen or silicon injections, deep dermal injections of microspheres of PLLA stimulates an inflammatory tissue response that leads to neocollagenesis, gradual dermal fibroplasia and increased dermal thickness [2,4,16,17,20]. The inflammatory response is initiated by the slow degradation of the PLLA microspheres that are hydrolyzed into lactic acid monomers by macrophages, mast cells, and lymphocytes. This leads to an influx of fibroblasts with the deposition of type III collagen that is eventually replaced by type I collagen fibers [5]. Because the mechanism of action is based on the stimulation of collagen production, the effects are not immediate. However, the delayed bio-stimulatory effect can result in a more favorable outcome with a thicker dermis and improved skin texture [7]. The results appear to be as effective as and longer lasting than fat injections at improving contour irregularities [1,4]. Initially, the major risk of PLLA was the potential for granuloma formation [2]. This risk has been greatly reduced by increasing the reconstitution volume from 3ml to 5ml with deionized water and allowing the reconstituted PLLA to sit overnight before use [5,20].

In practice, PLLA is FDA approved for treating HIV associated lipoatrophy of the face and for facial cosmetic issues such as wrinkles, skin folds, volume deficiency, and nasolabial fold contour deficiencies [8,20]. Studies have shown that PLLA is a reliable and long-lasting treatment for these cosmetic issues with an associated high patient satisfaction rate [21]. Some examples of off label use include treatment of acne and varicella scars, chest wall “step-off” abnormalities following breast reconstruction, prominent facial asymmetry/Romberg syndrome, soft tissue volume deficiency on the dorsum of the hands, gluteal enhancement, neck, abdomen, and post-operative soft tissue loss after melanoma excision [1,7,8].

One of the more interesting uses of PLLA was seen in a case report by Schulman et al where the authors treated a “step-off” abnormality between the contour of the right breast implant and ribcage of a thin 63-year-old woman [4]. After 6 months of failed attempts at surgical correction with acellular cadaveric dermis, the decision was made to use PLLA to induce production of collagen to add volume and smooth the deformity [4]. The patient received 2 vials (367.5 mg each) of PLLA monthly for 4 months that was injected into the subcutaneous tissue and deep dermal layers. By the final treatment a significant esthetic improvement had been seen and was not diminished by her last follow up appointment at 9 months [4]. This shows the potential usefulness that PLLA has in treating soft tissue deformities as a minimally invasive alternative to surgical interventions.

The treatment of acne and varicella scars is a particular area of interest due to the historic difficulty in treating these scars. They previously required multiple treatments with several different modalities before improvement was seen [22]. However in a case report by Sadick and Palmisano, PLLA was used to treat a 60-year old white woman with significant acne scars on bilateral cheeks. In this study, improvement was seen within 24 months in this patient with moderate-to-severe scarring. Even after just 7 treatments with 4-week intervals, there was a significant reduction in scar size [22]. Their results matched the outcomes that were described in an open-label study that investigated the use of PLLA for acne and varicella facial scars [8,23]. It was also hypothesized that the rapid improvement in the severity of scars was due to the subcison of the fibrous bands at the base of the scars by the needle itself that allowed the depressed scars to elevate, rather than solely the collagen stimulation by the PLLA.

**Calcium Hydroxylapatite**

Calcium Hydroxylapatite’s (CHA) mechanism of action is very similar to PLLA with neocollagenesis and subsequent filling effect that strengthens the dermis after a deep dermal injection [2]. CHA is composed of inorganic calcium hydroxylapatite microspheres in a gel solution composed of sterile water, glycerin, and carboxymethylcellulose [2,3,6,11,17]. CHA stimulates an
inflammatory response much like the PLLA response [3]. CHA injections also share the long-term effects of dermal remodeling that PLLA has. Punch biopsies taken 4 and 9 months after CHA injections showed an increase in elastin and collagen 1 and 3 with an increase in overall thickness, elasticity, and pliability of the skin [10,11,18]. CHA has FDA approval for the treatment of HIV lipoatrophy and facial volume deficiency, as well as for dorsal hand filling [18]. Many dermatologists are also using CHA for off-label treatments.

These treatments include replenishing volume loss in the deep fat compartments of the midface and submental area. Results have been positive with deep injections [3]. It has been shown to replenish lost volume to the mid and lower face which creates a smooth and youthful jawline [6]. Other treatments that have been successful are the filling of periorbital hollows, dark circles, and lower eye bags and for the treatment of acne scars [22,24]. One advantage of CHA compared to PLLA is that the volume enhancing results appear more instantaneous because of the gel component of the injection. The bio-stimulatory effect on collagen deposition can persist for up to 12 months [9].

Some dermatologists have also begun using CHA for treating other non-facial volume loss and skin laxity. Diluted superficial injections of 1:2 and 1:4 with sterile saline have been effective in treating the neck, upper arms, buttocks, thighs, and abdomen [7,23]. One single-armed, clinical study of 20 healthy Caucasian woman (ages 28-67) showed significant improvement in skin flaccidity in these areas after 5 weeks of treatment [10]. CHA has shown promising results with high patient satisfaction rates in the upper arm specifically, with ultrasound showing increased dermal thickness and a decreased skin flaccidity and improved volume after only 2 treatments in some patients [11,18]. CHA has been used in treating stretch marks, as well, with a decrease in the appearance of red and white striae when combined with topical ascorbic acid [23]. There have also been some studies that have investigated CHA’s effectiveness in treating cellulite. When combined with MFU-V (micro focused ultrasound with visualizations) there have been statistically significant improvements in cellulite severity [23].

Topical treatments have also gained popularity in the treatment of cellulite. They often consist of either a monotherapy or a combination of retinoic acid, methylxanthines, laser therapy, and carboxytherapy [26]. These treatments effectively camouflage the rippled appearance of the skin through temporary tightening effects. Retinoic acid increases collagen production with a longer-term effect on the skin strength [26]. Retinoic acid treatments saw major epidermal changes weeks after treatment with increased fibroblasts, collagen levels, and decreased metalloproteinases. When combined with caffeine, there was a significant decrease in cellulite severity [14]. Dietary supplementations with collagen peptides have also shown stimulatory effects in dermal cellular

Treatment of Cellulite

Cellulite is a common cosmetic issue for many people, with estimates of up to 85% of women over the age of 20 affected by some degree of cellulite [14,26]. Cellulite is often described as ripples and dimples of skin in the thighs and buttocks. While often associated with obesity, cellulite is likely a result of underlying adipose tissue herniating through altered or damaged subcutaneous fibrous connective tissue [15,27,28]. In addition, many patients with normal BMIs can present with cellulite of varying severities [27,29]. Multiple factors are hypothesized to contribute to the development of cellulite including persistent low-grade inflammation, microvascular dysfunction leading to tissue edema, lymphostasis, localized adipocyte hypertrophy, collagen denaturation, dermal thinning, tissue laxity, and altered orientation of fibrous septa connecting the reticular dermis to the deep fascia [15,25,27,28,30,31]. Differences in microanatomy may explain why more women than men suffer from cellulite.

In women, the superficial adipose layer has larger fat-cell chambers than men, which may increase the amount of fat that can herniate through weakened dermal connective tissue [27]. Differences between men and women in the orientation of the fibrous septa connecting the deep fascia to the reticular dermis may also contribute. In men, the septa are oriented in a crisscrossing fashion, while in women there is a more perpendicular orientation which leads to localized points of tension and the dimpling characteristic of cellulite. In various studies, it has been shown that a greater percentage of perpendicular septa correlates with the severity of cellulite [14,26,27,29,31]. For these reasons, therapies, such as PLLA and CHA, that target the dermis and subcutaneous tissue may be beneficial as a minimally invasive treatment for cellulite [25].

The mainstay of therapy for cellulite has historically been weight-loss and liposuction. However, neither have proven to be an effective treatment, with some cases worsening in severity [31]. Many new non-invasive treatments have been developed to attempt to target various aspects of cellulite [26,27]. Radiofrequency therapy, for example, causes an increase in local metabolism due to the heat produced by radiofrequencies in the subcutaneous fat. A subsequent increase in the microcirculation also enhances lymphatic drainage and breaks down erythrocyte adhesions [32]. It has resulted in improved body shaping in the outer and inner thighs, reduction in cellulite, and the induction of new collagen production, improving the dermal strength and decreasing skin laxity [27,30,32]. Massage therapy has also shown promising results by encouraging the movement of interstitial fluid and improving lymphatic drainage. One study demonstrated an enhanced presence of longitudinal collagen bands in areas where distortion and disruption of adipocytes were noted [14].

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metabolism leading to improved biosynthesis of extracellular matrix proteins that leads to restored dermal structure [25]. More invasive techniques are used to treat cellulite, as well. Manual subcision of fibrous bands with needles or blades has shown positive results in decreasing dimpling in cellulite [26]. Pulsed 1440-nm laser treatment has also been shown to break down these fibrous bands and induce an inflammatory response that increases collagen remodeling with more collagen and elastin production [31].

These treatments, especially in combination, help address the lymphatic stasis, remove excess lipids, and break fibrous bands. In addition, many induce neocollagenesis and strengthen the dermis. We believe that the treatment of cellulite with either CHA or PLLA will be successful at decreasing the severity of cellulite in patients. In fact, in some early studies with PLLA, there was at least a one-grade loss of volume and cellulite improvement in 80% of cases based on the Global Aesthetic Improvement Scale [7]. These treatments may also serve as another form of subcision of fibrous bands while inducing production of new collagen. This will ideally lead to even longer lasting effects than the current treatment methods.

Buttock Enhancement

Another area of interest for the use of bio-stimulatory injections is as a non-invasive option for buttock enhancement. Lately, buttock enhancement has become one of the most requested body enhancements with a 58% [33] increase in the number performed in 2013 to 2015. Approximately 20,000 Americans underwent a buttock enhancement procedure in 2015 [33,34]. Like other areas of the body that have been discussed so far, gluteal ptosis is due to changes in fat distribution, gravitational force, loss of musculature, and other factors such as pregnancy and dietary disorders [34]. The mainstay of treatment is surgical augmentation aimed at improving volume and posterior projection, as well as improving symmetry. This includes procedures that resect excess tissue such as liposuction, lipofilling/fat grafting, buttock implants with lipofilling, local flaps, and polypropylene strip gluteal suspension [33,34]. Other techniques have been increasing in popularity, as well, including local tissue rearrangement and hyaluronic acid gel injections [33]. Because most of these treatments are fairly invasive, there are some rare, significant complications that can be associated. For example, wound dehiscence, implant revision, implant removal, implant palpability, implant displacement, and capsular contracture have been reported [33]. Even the less invasive procedures, such as fat grafting, can lead to seromas at the donor sites and fat embolism [33]. As of today, fat grafting is associated with the lowest rate of complications at 10.5% [33] and is very effective at shaping the buttocks and correcting asymmetries and volume deficiencies [33]. However, there has been an increasing use of hyaluronic acid injections that have shown to be as effective and safer for temporary gluteal enhancement [33]. In some studies, it has been shown to have a positive patient rated improvement and satisfaction rate in only one to two treatments with results lasting about 24 months with a 400mL injection [33]. Due to the success that hyaluronic acid injections have in patient satisfaction, as well as the positive results that have been seen in providing long term filling effects in other parts of the body, bio-stimulatory injectables may also serve as a useful tool for non-invasive gluteal enhancement. Being able to provide a long lasting, non-invasive filling effect that strengthens the dermis, provides an improvement in elasticity, and decreases skin laxity offers patients a promising alternative to surgery [35].

Gluteal Enhancement in Practice

With the promising results that have been seen recently in the literature, we have begun using bio-injectables, specifically CHA, in our own practice forgluteal enhancement with great results thus far. We have developed a very effective procedure that promotes good results with minimal discomfort during and after treatment. The first step in the procedure is to evaluate the grade of cellulite by marking each cellulite band with a marker as the patient stands and contracts the gluteus muscles. The depth of penetration of the band determines the grade as mild, moderate, or severe or the depth as shallow, medium, or deep to determine the aggressiveness of the treatment. The initial markings and evaluation can be seen in Figure 1 which was taken with arms elevated and folded to frontal waistline.

Figure 1: Patient before treatment with Radiesse. Each cellulite band is marked with a marker while the patient stands and contracts the gluteus muscles.

The next step is to then scrub the patient's buttocks twice with a topical antiseptic followed by anesthetizing the entry point superior to the trochanteric spot. An 11-inch blade is then used to create a small slit to introduce an infiltrator. We then use a
mosquito clamp to expand the opening to the subcutaneous tissue. A previously prepared tumescent fluid (500cc of Ringers Lactate solution plus 1% lidocaine and 1:100,000 epinephrine for a 0.1% lidocaine concentration) is injected in a fanning fashion using an infiltrator. Once the site is anesthetized, Capistrano and/or Keil cobra cannulas are used to break the cellulite bands with strong long strokes in multiple directions. The excess fluid is then drained from the entry points following successful breakage of the bands. Lastly, we inject 6cc of CHA that is reconstituted with sterile 6cc of lido without epinephrine into the upper buttock area in equal parts bilaterally. The buttocks are then manually massaged, and the entry points are dressed with absorbing material.

As can be seen in Figures 2 and 3, which are taken one week and 6 weeks after treatment respectively, we have had very positive results with the new procedure. This procedure offers a less invasive way to treat cellulite that decreases the discomfort during and after treatment compared with previous treatments and requires no analgesic therapy.

Figure 2: Patient one week following Radiesse injection treatment. Patient is standing while contracting the gluteus muscles.

Figure 3: Six weeks following Radiesse treatment. Patient standing while contracting the gluteus muscles.

**Conclusion**

Since their introduction for the treatment of HIV-associated lipoatrophy of the face, the use of bio-stimulatory injectables Poly-L-Lactic Acid (Sculptra™) and Calcium Hydroxylapatite (Radiesse™), has increased significantly with positive results. They are now used for treating cosmetic facial aging symptoms such as age-associated lipoatrophy, wrinkles, and redistribution of soft tissue with positive patient satisfaction and long-lasting effects. They have demonstrated, due to a foreign body-like reaction, an increase in the production of collagen that leads to a strengthening of the dermis as well as a gradual filling effect in treatment regions. This makes them beneficial in treating acne scars, stretch marks, dorsal hand aging lipoatrophy, skin laxity in upper extremities and abdomen, filling in “step-offs” in breast implants, and in treating cellulite. In the treatment of cellulite and for gluteal enhancement, we believe they have the potential to provide long lasting results through a less invasive procedure.

**References**


