Title: IMPLANTS FOR SCULPTING, AUGMENTING OR CORRECTING FACIAL FEATURES SUCH AS THE CHIN

Abstract: An injectable device, comprising a hyaluronic acid-based composition, useful for long lasting facial sculpting and correction of facial features, for example, for augmenting and shaping the profile, including for example, the chin, jawline or the nose, in a human being is provided. Methods of treatment are also provided.
IMPLANTS FOR SCULPTING. AUGMENTING OR CORRECTING FACIAL FEATURES SUCH AS THE CHIN

by Jean Xavier Roca Martinez and Aurore Ayglon

[0001] The present invention generally relates to injectable compositions and more specifically relates to injectable implants for adding structure and contour to the lower face.

[0002] Dermal fillers are injectable, biocompatible compositions which are well known to correct wrinkles and folds and add volume to the face. Hyaluronic acid (HA) is still considered by many to be one of the most desirable dermal fillers in that it does not pose the risk of an allergic reaction and it is temporary and reversible. The great majority of hyaluronic acid-based dermal fillers have been specifically developed for treating wrinkles and folds in skin. To be useful for facial contouring or substantial volumizing, it would be advantageous to increase the bulking effect of the compositions, also referred to as “lift”. It would also be advantageous to maximize resistances of the compositions to shear and normal deformation happening in the soft tissues of the face. One of the drawbacks of maximizing these resistances, for example, elasticity and cohesivity, is that it is expected that in doing so, the viscosity of the compositions will increase to the point that they become difficult to inject with a thin needle.

[0003] There is therefore a great need for an injectable HA based implant that is specifically designed to be effective in adding substantial volume to the face, for example, for contouring the lower face, for example, for augmenting or correcting the chin, for example, for correction of chin retrusion, or for example, for augmenting or correcting the nose. It would be highly advantageous if such an implant, despite, its high viscosity, would remain easy to inject with a thin needle.

[0004] The shape of the chin has long been recognized as an important feature of the face that elicits a strong aesthetic perception that tends to be associated with personality traits of an individual. A deficient chin that lacks projection is commonly
labeled a "weak chin" while prominent chins are labeled "strong chins", both implying strength of personality.

[0005] Several studies have suggested that faces with average proportions are viewed as the most attractive and that small features including a small chin are interpreted as attractive in females while the expanded chin and jaw, as a result of maturation, are interpreted as attractive in males. The appearance of the chin is a determinant of perceived attractiveness and can even influence an individual's psychosocial well-being.

[0006] Chin augmentation is conventionally performed by surgically placing a permanent implant above the jaw. The procedure is currently among the top aesthetic surgical procedures performed, based on the American Society for Aesthetic Plastic Surgery (ASAPS), and has increased 71% since 2010.

[0007] A retrusive chin can be the result of changes in growth of the lower third of the face during maturation, trauma, or facial aging, the latter of which may exacerbate the deformities or asymmetries caused by the former two. The shape of the mandible affects the mouth, chin, and neck. As an individual ages, the reduction in skeletal support of this region makes soft tissue atrophy prominent, exaggerating jowls, decreasing chin protrusion, and making the jawline look weak. Chin deformities are among the most common bony abnormalities of the face, the most common of which is horizontal microgenia characterized by the presence of normal vertical height with a retruded bony chin.

[0008] As the mandible and chin make up the framework of the lower face, augmentation methods to treat age-related chin retrusion and contour changes of the chin area or to treat microgenia have been explored for decades. Where the approach in correcting chin retrusion is to add volume, treatment methods have included chin implants, genioplasty, and injection of silicone and semi-permanent fillers, such as polymethylmethacrylate microspheres, and calcium hydroxyapatite. However, all of these treatment methods have drawbacks. For example, chin implants and genioplasty involve painful surgery that may not result in correction of chin retrusion and aesthetic
blending of the area. This approach may exacerbate bone resorption and infection, resulting in the need for implant removal. Injection of semi-permanent fillers have trade-offs between volumizing capacity and adverse events associated with semi-permanent fillers.

SUMMARY OF THE INVENTION

[0009] Accordingly, an injectable implant is provided for facial sculpturing, for example, for augmenting, correcting, restoring or creating volume in the chin and other facial features in a human being.

[00010] The present invention provides temporary, reversible, HA-based structural gels manufactured specifically to provide a safe, minimally invasive method to create facial volume or facial contours. The present implants provide improved volumizing and lift properties relative to other HA-based injectables, due to a combination of mechanical properties including high elasticity and high cohesivity, while still being easily injectable with a thin needle. The present implants may be used for injection into the subcutaneous and/or supraperiosteal space. In many embodiments the implants are moldable after injection, and therefore permit sculpting, contouring, and shaping across the injected areas, for example, the chin and jaw area.

[00011] The implants generally comprise a composition comprising a hyaluronic acid (HA) crosslinked with a crosslinking agent selected from the group consisting of 1,4-butanediol diglycidyl ether (BDDE), 1,4-bis(2,3-epoxypropoxy)butane, 1,4-bisglycidyloxybutane, 1,2-bis(2,3-epoxypropoxy)ethylene and 1-(2,3-epoxypropyl)-2,3-epoxycyclohexanethi. In some embodiments, the implants generally comprise a composition comprising a hyaluronic acid (HA) crosslinked with BDDE. The compositions are suitable for injection, for example, through a fine gauge needle, and are capable of augmenting, correcting, or creating volume or lift in the face, for example, the lower face, for example, the chin or jaw, or for the midface, for example, the nose.
[00012] In some embodiments, the HA concentration is greater than 20 mg/g. In some embodiments, the HA concentration is about 21 mg/g, or about 22 mg/g, or about 23 mg/g, or about 24 mg/g, or about 25 mg/g, or about 26 mg/g, or about 27 mg/g, or about 28 mg/g, or about 29 mg/g, or about 30 mg/g or greater. In other embodiments, the composition has an HA concentration of between 22.5 mg/g to 27.5 mg/g, for example, 25.0 mg/g.

[00013] In some embodiments the method adds volume and lift to the chin or jawline or nose of the patient for a period of time in the range of about 9 months to about 24 months after the administration or injection into the chin or jawline of the patient. The composition may be moldable, for example, by physical manipulation of the tissue near the implant for a period of time after injection. The compositions may have a setting time, when the composition is no longer moldable and substantially retains its shape for the duration of the implant, within about 24 to about 48 hours after being implanted or injected.

[00014] In some embodiments, the compositions further include an anesthetic agent, for example, lidocaine HCl. For example, the compositions may include about 0.3% w/w lidocaine HCl.

[00015] In some embodiments, compositions are made with a mixture of low molecular weight hyaluronic acid and high molecular weight hyaluronic acid. For example, the crosslinked hyaluronic acid may be made from about 50% and about 100% of a low molecular weight hyaluronic acid prior to being crosslinked with the crosslinking agent. In some embodiments, the crosslinked hyaluronic acid is made from about 70% to about 90% of a low molecular weight hyaluronic acid prior to being crosslinked with the crosslinking agent. In some embodiments, the crosslinked hyaluronic acid is made from about 90% of a low molecular weight hyaluronic acid prior to being crosslinked with the crosslinking agent.

[00016] Using primarily a low molecular weight HA prior to crosslinking, for example about 50% or greater, for example, about 70% or about 90% low molecular weight HA, rather than using primarily a high molecular weight HA, produces a more robust, longer
lasting, moldable hydrogel, having a higher cohesivity and elasticity, and more specifically suitable for facial sculpturing and augmentation by means of subcutaneous or supraperiosteal injection.

[00017] In some embodiments, the HA has a degree of crosslinking of between about 4% and about 12%. For example, the HA has a degree of crosslinking of about 4%, or about 6%, or about 8%, or about 10%. In some embodiments the HA has a degree of crosslinking of about 6.5%. In other embodiments, the HA has a degree of crosslinking of about 7.5%, or about 8.5%, or about 9.5%, or about 10.5%.

[00018] In another aspect of the invention, methods for correcting chin retrusion in a patient are provided. The methods generally comprise supraperiostally administering in the chin of the patient, an effective amount of a composition comprising BDDE-crosslinked hyaluronic acid (HA), the HA having a degree of crosslinking of about 10%, and having a HA concentration of greater than 20 mg/g. For example, in a preferred embodiment, the HA concentration is about 25 mg/g.

[00019] In a specific embodiment, the compositions comprises low molecular weight hyaluronic acid (NaHA) crosslinked with about 10% BDDE (w/w), and formulated to a concentration of about 25 mg/g with 0.3% lidocaine hydrochloride (w/w) in a phosphate buffer, pH 7.2, and supplied in a 1 ml_ COC (cyclic olefin copolymer) syringe.

[00020] The compositions are extrudable through a fine gauge needle, for example, a needle having a gauge of 25G, 26G, 27G, 28G, 29G or 30G. In a specific embodiment, the needle is a needle of 27 gauge X 13 mm / 27 G1/2 X 26mm.

[00021] An extrusion force is the force (in Newtons N) needed to extrude the composition from its syringe at a certain rate. For example, with the supplied 1 ml_ COC syringe and a TSK 27G X 13mm needle, the extrusion force of some of the compositions of this invention can be between about 4N and about 15N at 13 mm/min, which is considered as very low. For example, the extrusion force can be between about 7N and about 12N, and preferably between about 8N and about 10 N.
In another aspect of the invention, methods are provided for contouring or correcting a facial feature, for example, a retruded chin, of an individual. The methods comprise, for example, the step of subdermally administering into a treatment area of the patient, an effective amount, for example, about 1.0 ml, or more, for example, about 2.0 ml or more, for example, about 3.0 ml or more, for example, 4.0 ml, of a composition of the invention. The facial feature to be improved or contoured may be a chin, for example, a retruded chin of a patient. The treatment area may include an area selected from the group consisting of the pogonion, the mentum, the left pre-jowl sulcus, the right pre-jowl sulcus, and the sublabial crease. The treatment may comprise administering the composition into two or more of the treatment areas.

Each and every feature described herein, and each and every combination of two or more of such features, is included within the scope of the present invention provided that the features included in such a combination are not mutually inconsistent.

BRIEF DESCRIPTION OF THE DRAWINGS

Figure 1 shows a facial profile and landmarks for calculating G-Sn-Pog angle of a patient.

Figure 2 shows the Burstone Angle of an average chin.

DETAILED DESCRIPTION

Certain terms as used in the specification are intended to refer to the following definitions, as detailed below. Where the definition of terms departs from the commonly used meaning of the term, applicant intends to utilize the definitions provided below, unless specifically indicated.

The term "about" in the context of numerical values will be readily understood by a person skilled in the art, and preferably means that specific values may be modified by +/- 10%. As regards endpoints of ranges, the modifier "about" preferably means that the lower endpoint may be reduced by 10% and the upper endpoint
increased by 10%. It is also contemplated that each numerical value or range disclosed in this application can be absolute, i.e. that the modifier "about" can be deleted.

[00028] All numbers herein expressing "molecular weight" of HA are to be understood as indicating the weight average molecular weight (Mw) in Daltons.

[00029] The molecular weight of HA is calculated from an intrinsic viscosity measurement using the following Mark Houwink relation:

\[
\text{Intrinsic Viscosity (L/g)} = 9.78 \times 10^{-5} \times \text{Mw}^{0.690}
\]

[00030] The intrinsic viscosity is measured according to the procedure defined European Pharmacopoeia (HA monograph N°1472, 01/2009).

[00031] Unless stated otherwise, the molecular weight refers to the weight average molecular weight (Mw). The HA used to make the present compositions may comprise a mixture of high molecular weight HA, low molecular weight HA, and/or medium molecular weight HA, wherein the high molecular weight HA has a molecular weight greater than about 2,000,000 Da (or an intrinsic viscosity greater than 2.2 L/g) and wherein the low molecular weight HA has a molecular weight of less than about 1,000,000 Da (or an intrinsic viscosity lower than 1.4 L/g. For example, the high molecular weight HA in the present compositions may have an average molecular weight in the range about 2 MDa to about 4.0 MDa, for example, about 3.0 MDa (2.9 L/g). In another example, the high molecular weight HA may have an average molecular weight of between about 2.4 MDa to about 3.6 MDa, for example, about 3.0 MDa. The high molecular weight HA may have an intrinsic viscosity greater than about 2.2 L/g, for example, between about 2.5 L/g to about 3.3 L/g.

[00032] Low molecular weight HA can have a molecular weight of between about 200,000 Da (0.2 MDa) to less than 1.0 MDa, for example, between about 300,000 Da (0.3 MDa) to about 750,000 Da. (1.1 L/g), up to but not exceeding 0.99 MDa (1.4 L/g). The low molecular weight HA may have an intrinsic viscosity of less than about 1.40 L/g, for example, between about 0.6 L/g and about 1.2 L/g.
Preferably, there is no overlap between the molecular weight distribution of the low and high molecular weight HA materials.

Preferably, the mixture of the low molecular weight HA and high molecular weight HA has a bimodal molecular weight distribution. The mixture may also have a multi-modal distribution.

In one aspect of the invention, the compositions comprise HA having a high molecular weight component and a low molecular weight component, and the high molecular weight component has a weight average molecular weight at least twice the weight average molecular weight of the low molecular weight component.

"Degree of crosslinking" as used herein refers to the intermolecular junctions joining the individual HA polymer molecules, or monomer chains, into a permanent structure, or as disclosed herein the soft tissue filler composition. Moreover, degree of crosslinking for purposes of the present disclosure is further defined as the percent weight ratio of the crosslinking agent to HA-monomeric units within the crosslinked portion of the HA based composition. It is measured by the weight ratio of crosslinker to HA monomers.

"Uncrosslinked HA" as used herein refers to individual HA polymer molecules that are not crosslinked. Uncrosslinked HA generally remains water soluble. An uncrosslinked HA fraction may optionally also be included in the compositions, for example, to act as a lubricant and facilitate injection into the facial tissues. Such a composition may comprise an uncrosslinked HA fraction where the added uncrosslinked HA is present at a concentration between about 0.1 mg/g and about 3 mg/g. Preferably, the uncrosslinked HA may be present at a concentration between about 0.2 mg/g and about 1.5 mg/g.

In other embodiments, no uncrosslinked HA is present in the gels, or at least no uncrosslinked HA is added to the gels to act as a lubricant.

The compositions described herein display a high level of elasticity, expressed as a value of elastic modulus (G') measured by oscillation rheology with a
strain of 0.8%, using a cone-plate system and measured over a range of frequencies. In some embodiments, the elastic modulus of the compositions measured at 5Hz frequency are from about 500 Pa to about 900 Pa. This is considered as high elasticity in the context of HA-based dermal fillers and contributes to the lifting effect by making the implant more resistant to shear deformation.

[00038] Cohesivity refers to the capacity of the gel to stay attached to itself, for example, meaning the resistance to cutting and the ability to elongate or compress the gel without it separating into pieces. The cohesivity of the gels according to the present invention can be quantified as follows (cf. Derek Jones "Injectable Fillers: Principles and Practice", Wiley, 2011, Chapter 3). A small sample of the gel (e.g. 1 ml) is placed onto the plane surface of a rheometer. The sample is placed such that it forms a little heap. A moveable upper plate is placed onto the sample so that the sample is fully covered, e.g. when looking at the plate in a direction perpendicular to the surface of the rheometer, the sample cannot be seen. In order to ensure this, one must chose a plate size that is larger than the sample size. Ideally, the center of the plate is placed over the sample. Typically, for 1 ml of gel material, a 25mm diameter upper plate is used.

[00039] In the next step of the measurement, one then adjusts the gap between the moveable plate and the surface to 2.5 mm. While slowly and steadily moving the plate from this initial position towards a gap width of 0.9 mm within 2 min one records the force (Fn) exerted by the sample in normal direction on the plate.

[00040] Once a gap width of 0.9 mm is reached, the system is allowed to relax for 12 minutes. During this time, the measurement is continued. Five measurements are done. To normalize the forces measured, all 5 initial Fn values measured when the test starts are averaged (arithmetic mean) and this resulting average is subtracted from all other data points. The maximum force at the end on the compressive part of this test (when reaching the minimal 0.9mm gap width between the upper plate and the plane) is called the compression force and is the characteristic value for determining the cohesivity of the gel.
Specifically, a force of 20 gmf (0.1962 N) or more indicates a cohesive material in the sense of the present invention. Gels with lower compression force values are generally not considered cohesive in the context of the present invention. The accuracy of this measurement is in the order of ±5 gmf. In the context of this invention, the injectable formulation has a high cohesivity of at least about 60 gmf, for example about 60 to about 200 gmf. For example, in a preferred embodiment, cohesivity is between about 60 and about 100 gmf, which will give to the implant a high resistance to pressure and normal forces in the soft tissues of the face.

In the context of a dermal filler, the cohesivity as defined above will contribute to the lift capacity (clinically called the volumizing / bulking effect) provided by the gel clinically, along with its elastic modulus G'. While cohesive gels can show a good volumizing effect, non-cohesive or weakly cohesive materials with a similar elastic modulus exhibits lower lift capacity due to the non-cohesive gel material spreading more than a more cohesive material when submitted to vertical compression. In the context of this invention, the compositions exhibit both high levels of elastic modulus and high levels of cohesivity, to maximize the lifting effect upon implantation.

In certain advantageous, exemplary embodiments, the present implants or fillers generally comprise a cohesive, sterile composition which is implantable subdermally or supraperiostially into the chin area, nose or jawline of the patient in need thereof, for example a patient desiring an improved facial profile or stronger chin. The composition generally comprises a crosslinked hyaluronic acid (HA) crosslinked with 1,4-butanediol diglycidyl ether (BDDE); and the HA concentration of the composition is greater than 20 mg/g. For example, in some embodiments, the HA concentration is about 22.5 mg/g, or about 25 mg/g, or about 27.5 mg/g. The HA used for crosslinking may be made with a mixture of low molecular weight hyaluronic acid and high molecular weight hyaluronic acid. In some embodiments, the compositions have an elastic modulus between about 500 Pa and about 900 Pa at 5Hz, and a cohesivity above about 60 gmf. Advantageously, in some embodiments, the compositions exhibit an extrusion force between about 4N and about 15N, for example, between about 8N and about 10 N, at 13 mm/min using a 1 ml_ COC syringe and a 27G x 13mm needle.
In one aspect of the invention, injectable HA-based implants having an improved lift capacity, relative to commercial HA-based dermal fillers, are provided. The present implants are, in some instances in the present disclosure, referred alternatively as dermal fillers and subdermal fillers. The implants and fillers of the present invention are based on hyaluronic acids (HA) and pharmaceutically acceptable salts of HA, for example, sodium hyaluronate (NaHA). Methods of making these compositions, and methods of use of these compositions, are also provided.

As used herein, hyaluronic acid (HA) can refer to any of its hyaluronate salts, and includes, but is not limited to, sodium hyaluronate (NaHA), potassium hyaluronate, magnesium hyaluronate, calcium hyaluronate, and combinations thereof. Both HA and pharmaceutically acceptable salts thereof can be used in this invention.

In addition, in embodiments with anesthetics, the concentration of one or more anesthetics is in an amount effective to mitigate pain experienced upon injection of the composition. The at least one local anesthetic can be selected from the group of ambucaine, amolanone, amylocaine, benoxinate, benzocaine, betoxycaine, buphenamine, bupivacaine, butacaine, butamben, butanilicaine, butethamine, butoxycaine, carticaine, chloroprocaine, cocaethylene, cocaine, cyclohexylcaine, dibucaine, dimethisouquin, dimethocaine, diperodon, dicyclomine, ecgonidine, ecgonine, ethyl chloride, etidocaine, beta-eucaine, euprocin, fenalcomine, formocaine, hexylcaine, hydroxytetracaine, isobutyl p-aminobenzoate, leucinocaine mesylate, levodaxadrol, lidocaine, mepivacaine, meprylcaine, metabutoxycaine, methyl chloride, myrtocaine, naepaine, octocaine, orthocaine, oxethazaine, parethoxycaine, phenacaine, phenol, piperocaine, piperidine, polidocanol, pramoxine, prilocaine, procaine, propanocaine, proparacaine, propipocaine, propoxycaine, pseudococaine, pyrrocaaine, ropivacaine, salicyl alcohol, tetracaine, tolycaine, trimecaine, zolamine, and salts thereof. In one embodiment, the at least one anesthetic agent is lidocaine, such as in the form of lidocaine HCl. The compositions described herein may have a lidocaine concentration of between about 0.1 % and about 5% by weight of the composition, for example, about 0.2% to about 1.0% by weight of the composition. In one embodiment, the composition has a lidocaine concentration of about 0.3% by weight (w/w %) of the composition. The
concentration of lidocaine in the compositions described herein can be therapeutically effective meaning the concentration is adequate to provide a therapeutic benefit without inflicting harm to the patient.

[00047] The present compositions may be manufactured by the steps of providing purified HA material for example, in the form of NaHA fibers; the HA material having a desired molecular weight, for example, a mixture of low molecular weight and high molecular weight HA at a desired ratio, hydrating the HA material; and crosslinking the hydrated HA material with a suitable crosslinking agent at the desired ratio to form a crosslinked HA-based gel. The gel may then be neutralized and swollen. If desired, a solution containing lidocaine, preferably an acidic salt of lidocaine chlorohydrate, may be added to form a HA/lidocaine gel. The gel may be homogenized, for example, by beating or mixing with a shear force. The homogenized composition may then be packaged in syringes. The syringes are then sterilized by autoclaving at an effective temperature and pressure. For example, the compositions are sterilized by autoclaving, for example, being exposed to temperatures of at least about 120°C to about 130°C and/or pressures of at least about 12 pounds per square inch (PSI) to about 20 PSI for a period of at least about 1 minute to about 15 minutes. The sterilized syringes are packaged along with a fine gauge needle for use by a physician.

[00048] More specifically, the initial raw HA material may comprise fibers or powder of NaHA, for example, bacterial-sourced NaHA fibers. Alternatively, the HA material may be animal derived, for example, from rooster combs. It is contemplated that the HA material may be a combination of raw materials including HA and at least one other polysaccharide, for example, another glycosaminoglycan (GAG).

[00049] In one method of manufacturing the compositions, pure, dry NaHA fibers are hydrated in an alkaline solution to produce an uncrosslinked NaHA gel. Any suitable alkaline solution may be used to hydrate the NaHA in this step, for example, but not limited to aqueous solutions containing sodium hydroxide (NaOH), potassium hydroxide (KOH), sodium bicarbonate (NaHC03), lithium hydroxide (LiOH), and the like. The resulting alkaline gel will have a pH above 7.5. The pH of the resulting alkaline gel can
have a pH greater than 9, or a pH greater than 10, or a pH greater than 12, or a pH greater than 13.

[00050] The next step in the manufacturing process may include the step of crosslinking the hydrated, alkaline NaHA gel with a suitable crosslinking agent. The crosslinking agent may be any agent known to be suitable for crosslinking polysaccharides and their derivatives via their hydroxyl groups. One particular suitable crosslinking agent is 1,4-butanediol diglycidyl ether (BDDE).

[00051] In another embodiment, the crosslinking of the HA is accomplished during hydration of the HA fibers, by hydrating the combined high and low molecular weight fibers in an alkaline solution containing a crosslinking agent, for example, BDDE.

[00052] The degree of crosslinking in the HA component of the present compositions is at least about 4% and is up to about 12% BDDE/HA, w/w, for example, about 10%, for example, about 8%, for example, about 6%, for example, about 4%. In a specific embodiment, the degree of crosslinking is about 6.5%. In some embodiments the HA has a degree of crosslinking of about 6.5%. In other embodiments, the HA has a degree of crosslinking of about 7.5%, or about 8.5%, or about 9.5%, or about 10.5%.

[00053] The hydrated crosslinked, HA gels may be swollen to obtain the desired HA concentration. This step can be accomplished by neutralizing the crosslinked, hydrated HA gel, for example by adding an aqueous solution containing of an acid, such as HCl. The gels are then swelled in a phosphate buffered saline (PBS) solution for a sufficient time and at a low temperature.

[00054] The gels may now be purified by conventional means such as, dialysis against a phosphate buffer, or alcohol precipitation, to recover the crosslinked material, to stabilize the pH of the material and to remove any un-reacted crosslinking agent. Additional water or a slightly alkaline aqueous solution can be added to bring the concentration of the HA in the composition to a desired concentration. In some embodiments, the HA concentration of the compositions is adjusted to above 20 mg/g, for example, to about 25 mg/g. In other embodiments, the HA concentration is adjusted
to yield an HA concentration of about 21 mg/g, about 22 mg/g, about 23 mg/g, about 24
mg/g, about 26 mg/g, about 27 mg/g, about 28 mg/g, about 29 mg/g, or about 30 mg/g.

[00055] In embodiments in which an anesthetic agent is to be included in the final
composition, such as lidocaine, the pH of the purified crosslinked HA gels may be
adjusted to cause the gel to become slightly alkaline such that the gels have a pH of
greater than about 7.2, for example, about 7.5 to about 8.0. This step may be
accomplished by any suitable means, for example, by adding a suitable amount of dilute
NaOH, KOH, NaHCO3 or LiOH, to the gels or any other alkaline molecule, solution
and/or buffering composition.

[00056] An effective amount of the anesthetic, for example, lidocaine, such as
lidocaine HCl, is then added to the purified crosslinked NaHA gels. For example, in
some embodiments, the lidocaine HCl is provided in a powder form which is solubilized
using water for injection (WFI). The gels are kept neutral with a buffer or by adjustment
with diluted NaOH in order that the final HA/lidocaine composition will have a desired,
substantially neutral pH. The final compositions including lidocaine may have a
lidocaine concentration of between at least about 0.1 % and about 5%, for example,
about 2% by weight of the composition, or in another example about 0.3%.

[00057] After the addition of the lidocaine HCl, or alternatively, during the addition of
the lidocaine HCl, the HA/lidocaine gels, or compositions, are homogenized to create
highly homogenous HA/lidocaine gels having a desired consistency and stability.
Preferably, the homogenization step comprises mixing, stirring, or beating the gels with
a controlled shearing force obtaining substantially homogenous mixtures.

[00058] After homogenizing the HA composition, an amount of uncrosslinked HA
solution or gel may be added to the composition to increase lubricity.

[00059] In some embodiments, no solution of uncrosslinked HA is added to the
composition after homogenization.

[00060] The compositions may then be introduced into syringes and sterilized.
Syringes useful according to the present description include any syringe known in the
art capable of delivering viscous dermal filler compositions. The syringes generally have an internal volume of about 0.4 ml to about 3 ml, more preferably between about 0.5 ml and about 1.5 ml or between about 0.8 ml and about 2.5 ml. This internal volume is associated with an internal diameter of the syringe which plays a key role in the extrusion force needed to inject high viscosity dermal filler compositions. The internal diameters are generally about 4 mm to about 9 mm, more preferably from about 4.5 mm to about 6.5 mm or from about 4.5 mm to about 8.8 mm. Further, the extrusion force needed to deliver the HA compositions from the syringe is dependent on the needle gauge. The gauges of needles used generally include gauges between about 18G and about 40G, more preferably about 25G to about 33G, or from about 25G to about 30G. For example, in some embodiments, the compositions are packaged in a 1 ml syringe and injected using a 27 G needle.

[00061] One preferable method of sterilization of the filled syringes is by autoclave. Autoclaving can be accomplished by applying a mixture of heat, pressure and moisture to a sample in need of sterilization. Many different sterilization temperatures, pressures and cycle times can be used for this step. For example, the filled syringes may be sterilized at a temperature of at least about 120°C to about 130°C or greater. Moisture may or may not be utilized. The pressure applied is in some embodiments depending on the temperature used in the sterilization process. The sterilization cycle may be at least about 1 minute to about 20 minutes or more.

[00062] Another method of sterilization incorporates the use of a gaseous species which is known to kill or eliminate transmissible agents. Preferably, ethylene oxide is used as the sterilization gas and is known in the art to be useful in sterilizing medical devices and products.

[00063] A further method of sterilization incorporates the use of an irradiation source which is known in the art to kill or eliminate transmissible agents. A beam of irradiation is targeted at the syringe containing the HA composition, and the wavelength of energy kills or eliminates the unwanted transmissible agents. Preferable energy useful include, but is not limited to ultraviolet (UV) light, gamma irradiation, visible light, microwaves, or
any other wavelength or band of wavelengths which kills or eliminates the unwanted transmissible agents, preferably without substantially altering or degrading the HA composition.

[00064] Preferably, the present compositions also remain stable when stored for long periods of time. For example, many of the present compositions have a shelf life of about 6 months, about 12 months, about 18 months, or about 24 months or greater, when stored at a temperature between about 2 to 25 degrees C. In a specific embodiment, the compositions are stable at a temperature of between 2 to 25 degrees C for a period of at least 18 months. In another specific embodiment, the compositions are stable at a temperature or between 2 to 25 degrees C for a period of at least 24 months.

EXAMPLE 1

MANUFACTURE OF AN INJECTABLE IMPLANT IN ACCORDANCE WITH AN EMBODIMENT OF THE INVENTION

[0001] Predried fibers of sodium hyaluronate (NaHA) (0.9 g) having a molecular weight of about 0.9 MDa is weighed out into a first receptacle.

[0002] Predried fibers of NaHA (0.1 g) having a molecular weight of about 3.0 MDa is weighed out into a second receptacle.

[0003] The two different grades of NaHA are combined and diluted into a 1% sodium hydroxide solution and mixed for one to two hours at between 20°C and 50°C to obtain a substantially homogenous, alkaline HA gel.

[0004] In a separate receptacle, the chosen crosslinking agent, 1,4-butanediol diglycidyl ether (BDDE), is diluted into a 1% sodium hydroxide solution to a final concentration of 10% BDDE (wt/wt).

[0005] To the alkaline HA gel was added 10% (wt/wt) BDDE (1 g of the previously prepared BDDE solution). The resulting mixture is mechanically homogenized.
[0006] The mixture is then maintained at 50°C for 3 to 4.5 hours.

[0007] The resulting crosslinked HA polymer is then immersed in a phosphate buffer (PB) containing hydrochloric acid to stabilize the pH.

[0008] The crosslinked HA polymer so obtained is then immersed in baths of phosphate buffer to remove unreacted crosslinking agent and HA, providing the purified hydrogel, wherein the degree of crosslinking is about 6.5%.

[0009] Optionally, dry HA material having a high molecular weight is hydrated in 1 liter of phosphate buffer to obtain an uncrosslinked HA gel. This uncrosslinked HA gel can be added to the crosslinked HA composition to represent up to 5% (w/w) of the total HA concentration.

[0010] The hydrogel obtained is then homogenized mechanically to ensure the final homogeneity, and packed into syringes which are sterilized in an autoclave.

[0011] The gel obtained is an injectable composition that can be administered subdermally or supraperiostally through a fine gauge needle (e.g. 27 Gauge). The composition is useful for restoring, contouring, or creating facial volume, for example, in the chin, jaw area, or nose of a person, as described elsewhere herein.

[0012] In one aspect of the invention, methods are provided for improving a patient's facial profile. For example, in some embodiments, methods are provided for changing a person's G-Sn-Pog facial angle, for example, for increasing a person's G-Sn-Pog facial angle. For example, in some embodiments, methods of treatment are provided for correcting chin retrusion in a patient. In some embodiments of the invention, the patient treated an initial pre-treatment G-Sn-Pog facial angle of less than about 165°. After the treatment, the patient has an increased G-Sn-Pog facial angle, that is, a facial angle greater than the initial pre-treatment facial angle. In one embodiment, the patient has a G-Sn-Pog angle of about 169° or greater after the step of administering. The G-Sn-Pog angle may be measured using conventional equipment and calculations, for example, may be based on calculations of facial angle derived from digital images of the patient, for example, using Canfield scientific facial imaging equipment. Figure 1 shows facial
profile and landmarks for calculating G-Sn-Pog angle of a patient, which can be used to
diagnose or determine the presence and/or degree of chin retrusion, using known
methods.

[00013] The methods generally comprise administering into at least one treatment
area of the face of the patient, an effective amount of a composition comprising BDDE-
crosslinked hyaluronic acid (HA), the HA having a degree of crosslinking of about 6.5%,
or about 10%, and having a HA concentration of greater than 20 mg/g.

[00014] In some embodiments, treatment methods are provided, the methods
comprising supraperiostally administering a composition, such as described herein, into
at least one treatment area of the face of a patient, wherein the patient has a G-Sn-Pog
facial angle of 145° to 165°. The facial angle value may be based on calculations of
facial angle derived from digital images of the patient, or using other techniques. In
accordance with some embodiments, the step of administering results in the patient
having an increased G-Sn-Pog angle relative to the patient's G-Sn-Pog facial angle
prior to the treatment, for example, immediately prior to the administering step. In some
embodiments, the patient has an increased G-Sn-Pog angle for a period of time in the
range of at least about 3 months, or more preferably, for at least about 6 months, for
example, for about 9 months to about 24 months, after the step of administering. For
example, the patient has an increased G-Sn-Pog angle for at least about 6 months, or
for at least about 9 months, or for at least about 12 months or for at least about 18
months or for at least about 24 months for after the step of administering.

[00015] In some embodiments, the treatment area is an area selected from the group
consisting of the pogonion, the mentum, the left pre-jowl sulcus, the right pre-jowl
sulcus, and the sublabial crease. The treatment may comprise administering the
composition into two or more of the treatment areas. The administration comprises
supraperiostally or subdermally injecting the compositions in an amount of between
about 0.5 ml and about 3.0 ml per treatment area. In some embodiments, the amount
injected into a given treatment area is no greater than 2.0 ml. In some embodiments,
the total amount injected in a single treatment session, over all treatment areas, is
between 2.0 mL to about 6.0 mL, for example, about 2.5 mL, about 3.0 mL, about 3.5 mL, about 4.0 mL, about 4.5 mL, about 5.0 mL, about 5.5 mL, or about 6.0 mL. In some embodiments, the amount administered into a single treatment session is about 4.0 mL or less.

Restoration and Creation of Volume in the Chin and Jaw

[00016] In one aspect, the present invention provides methods for restoring and creating volume in the chin and jaw, for example, in sculpting, shaping, and contouring across specific treatment areas of the face. The treatment areas may include one or more of the pogonion (the most projecting point on the anterior surface of the chin), mentum, (the lowest point on the chin), left and right pre-jowl sulci (left antegonion notch and right antegonion notch), and sublabial (mental) crease (the crease between the lower lip and the mentum).

[00017] The shape and projection of the chin contribute to the proportional balance of the face that underlies attractiveness. A chin lacking projection is commonly labeled a "weak chin" whereas prominent chins are labeled "strong chins" and imply strength of personality. Several studies have suggested that faces with average proportions are viewed as the most attractive and that juvenile features including a small chin are interpreted as attractive in females while a strong chin and jaw are interpreted as attractive in males. The appearance of the chin is a determinant of perceived attractiveness and can influence an individual's psychosocial well being.

[00018] Average proportions are dictated by analysis of a representation of facial profiles in a population and include the distances and angles between the nose, lip, and mentum. Several soft tissue landmarks have been used in cephalometric analysis to measure and diagnose chin protrusion and retrusion deviations from average facial parameters. The intersection of the upper facial and anterior lower facial components and the angle formed by the point on the glabella, subnasale, and pogonion (G-Sn-Pog) has been extensively analyzed to understand the average chin projection common among populations. The Burstone angle (Figure 2) has been defined as approximately
169° for the average chin, and the approximate angle (168° to 169°) has been confirmed in several studies.

[00019] Incrementally, deviations from the average chin result in the perception of facial unattractiveness. Analyzing the relationship between facial profile and perception of attractiveness shows that chin prominence plays a major role in this perception. To understand the relationship between the degree of chin prominence and attractiveness, a series of profile images altered in 2-mm increments from an idealized profile image was presented to a group of pretreatment orthognathic patients, clinicians, and laypeople. Subjects were asked to rate each image on a 7-point Likert scale ranging from extremely unattractive to extremely attractive. Ratings of perceived attractiveness decreased an average of 0.15 on the Likert Scale for each 2 mm of chin retraction and were apparent after 4 mm of change. The degree of chin retraction at which surgery was desired was 11 mm for patients and clinicians and 10 mm for laypeople. The most attractive image was that which displayed an ideal orthognathic profile with the soft tissue pogonion resting on the true vertical line.

EXAMPLE 2

METHOD FOR INCREASING THE G-SN-POG FACIAL ANGLE IN A SUBJECT HAVING CHIN RETRUSION OR A WEAK CHIN

[00020] A composition of the invention is administered as an injectable implant, by subdermal or supraperiosteal injection in the chin and/or jaw area of a 32 year old male subject. The subject complains he has a "weak chin". The doctor measures the subject's facial angle and determines that the a G-Sn-Pog angle of about 150°, which is substantially lower than the classic Burstone angle of the average chin (approximately 169°). The measurement is based on calculations of facial angle derived from digital images obtained using Canfield imaging equipment and software.

[00021] The doctor considers the subject's chin/jaw retraction to be amenable to correction with a treatment goal consistent with increasing chin projection horizontally (in the profile view), not chin lengthening or widening.
The doctor believes that he can provide the subject with a more attractive facial profile and a stronger jawline by using the implantable compositions described herein.

The subject undergoes three treatment sessions, including initial treatment, top-up treatment, and repeat treatment, as described below.

For each treatment, the treatment areas include at least one or more of the following treatment areas: the pogonion (the most projecting point on the anterior surface of the chin), the mentum (the lowest point on the chin), the left pre-jowl sulcus (left antignonion notch), the right pre-jowl sulcus (right antignonion notch), and/or the sublabial crease (the crease between the lower lip and the mentum).

The doctor implants no more than 2.0 mL into a single treatment area at any of the treatment sessions.

The initial treatment is performed on the subject as follows. The doctor uses aseptic skin preparation and administers anesthesia following his standard practice. The application of ice and topical anesthesia may reduce injection discomfort. Injectable anesthesia is limited to the treatment areas only is and administered with certainty not to distort the planned treatment areas.

Using needles (27 gauge x 13 mm / 27G ½") supplied with a kit, the doctor injects the compositions described herein subcutaneously and/or supraperiosteally to increase chin projection (horizontally in the profile view), as well as to aesthetically sculpt, contour, and shape, limiting treatment to the pogonion, mentum, pre-jowl sulci, and sublabial (mental) crease. The treatment goal is to increase chin projection (horizontally in the profile view) and achieve aesthetic chin contour. The doctor determines the appropriate injection volume up to about 4.0 mL for initial and possible top-up treatments combined.

The doctor gently molds the treated area using manual manipulation of the overlying tissue to achieve the desired facial contour.
A top-up treatment occurs approximately 30 days after the initial treatment if desired by the subject, or if in the doctor's opinion, optimal (full) increase in chin projection and/or aesthetic contouring was not achieved by the initial treatment. If a top-up treatment is performed, the volume of the administered composition as a combined total (initial treatment and top-up treatment) is between about 2.0 ml to about 4.0 ml). During this visit, the doctor evaluates the treatment areas for any localized reaction and discusses any reported symptoms. 3D facial digital images (frontal and profile images) are captured for objective calculation of the angle of chin retrusion. If the doctor determines at top-up follow-up visit that optimal (full) increase in chin projection or aesthetic contouring was not achieved after the initial treatment, then subject is advised that he may receive a top-up treatment.

A single repeat treatment is administered at a scheduled visit between months 18 and 24 if repeat treatment is warranted in the doctor's opinion and/or is desired by the subject. Injection volume for the chin does not exceed a total volume of 4.0 mL for the repeat treatment.

Although the invention has been described and illustrated with a certain degree of particularity, it is understood that the present disclosure has been made only by way of example, and that numerous changes in the combination and arrangement of parts can be resorted to by those skilled in the art without departing from the scope of the invention, as hereinafter claimed.

Unless otherwise indicated, all numbers expressing quantities of ingredients, properties such as molecular weight, reaction conditions, and so forth used in the specification and claims are to be understood as being modified in all instances by the term "about." Accordingly, unless indicated to the contrary, the numerical parameters set forth in the specification and attached claims are approximations that may vary depending upon the desired properties sought to be obtained by the present invention. At the very least, and not as an attempt to limit the application of the doctrine of equivalents to the scope of the claims, each numerical parameter should at least be

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construed in light of the number of reported significant digits and by applying ordinary rounding techniques.

[00033] Notwithstanding that the numerical ranges and parameters setting forth the broad scope of the invention are approximations, the numerical values set forth in the specific examples are reported as precisely as possible. Any numerical value, however, inherently contains certain errors necessarily resulting from the standard deviation found in their respective testing measurements. Notwithstanding that the numerical ranges and parameters setting forth the broad scope of the invention are approximations, the numerical values set forth in the specific examples are reported as precisely as possible. Any numerical value, however, inherently contains certain errors necessarily resulting from the standard deviation found in their respective testing measurements.

[00034] Specific embodiments disclosed herein may be further limited in the claims using consisting of or consisting essentially of language. When used in the claims, whether as filed or added per amendment, the transition term "consisting of" excludes any element, step, or ingredient not specified in the claims. The transition term "consisting essentially of" limits the scope of a claim to the specified materials or steps and those that do not materially affect the basic and novel characteristic(s). Embodiments of the invention so claimed are inherently or expressly described and enabled herein.

[00035] In closing, it is to be understood that the embodiments of the invention disclosed herein are illustrative of the principles of the present invention. Other modifications that may be employed are within the scope of the invention. Thus, by way of example, but not of limitation, alternative configurations of the present invention may be utilized in accordance with the teachings herein. Accordingly, the present invention is not limited to that precisely as shown and described.
What is claimed is:

1. A sterile composition, implantable subdermally or supraperiostially into the chin area, jawline or nose of a patient in need thereof, the composition comprising a crosslinked hyaluronic acid (HA) crosslinked with 1,4-butanediol diglycidyl ether (BDDE);
   wherein the HA concentration of the composition is greater than 20 mg/g;
   wherein the HA used for crosslinking is made with a mixture of low molecular weight hyaluronic acid and high molecular weight hyaluronic acid;
   wherein the composition has an elastic modulus between about 500 Pa and about 900 Pa at 5Hz
   wherein the composition has a cohesivity above 60 gmf;
   wherein the composition exhibits an extrusion force between about 4 N and about 15N at 13 mm/min using a 1 ml COC syringe and a 27G x 13mm needle.

2. The composition of claim 1 where the HA concentration is about 22.5 mg/g.

3. The composition of claim 1 where the HA concentration is about 25 mg/g.

4. The composition of claim 1 where the HA concentration is about 27.5 mg/g.

5. The composition of claim 1 where the HA used for crosslinking is a mixture containing at least 50% of low molecular weight HA.

6. The composition of claim 1 where the HA used for crosslinking is a mixture containing at least 70% of low molecular weight HA.

7. The composition of claim 1 where the HA used for crosslinking is a mixture containing about 90% of low molecular weight HA and about 10% of high molecular weight HA.
8. The composition of claim 1 wherein the cohesivity is between about 60 gmf and about 200 gmf.

9. The composition of claim 1 wherein the cohesivity is between about 60 gmf and about 100 gmf.

10. The composition of claim 1 where the extrusion force is between about 7 and about 12N at 13 mm/min using a 1 ml COC syringe and a 27G x 13mm needle.

11. The composition of claim 1 where the extrusion force is between about 8 and about 10N at 13 mm/min using a 1 ml COC syringe and a 27G x 13mm needle.

12. The composition of claim 1 wherein the composition further includes an anesthetic agent.

13. The composition of claim 1 wherein the composition further includes lidocaine hydrochloride.

14. A composition of claim 1 wherein the composition further includes about 0.3% lidocaine hydrochloride.

15. The composition of claim 1 wherein the HA has a degree of crosslinking of between about 4% and about 10%.

16. The composition of claim 1 wherein the HA has a degree of crosslinking of about 4%.

17. The composition of claim 1 wherein the HA has a degree of crosslinking of about 6%.
18. The composition of claim 1 wherein the HA has a degree of crosslinking of about 8%.

19. The composition of claim 1 wherein the HA has a degree of crosslinking of about 10%.

20. The composition of claim 1 wherein the HA has a degree of crosslinking of about 6.5%.

21. A method for correcting chin retrusion in a patient comprising:

   supraperiostally administering into at least one treatment area of the face of the patient, an effective amount of a composition comprising BDDE-crosslinked hyaluronic acid (HA), the HA having a degree of crosslinking of about 6.5%, and having a HA concentration of greater than 20 mg/g; the treatment area being selected from the group consisting of the pogonion, the mentum, the left pre-jowl sulcus, the right pre-jowl sulcus, and the sublabial crease,

22. The method of claim 21 wherein, prior to the administering, the patient has a G-Sn-Pog angle of less than about 165° based on calculations of facial angle derived from digital images of the patient.

23. The method of claim 21 wherein the administering results in the patient having an increased G-Sn-Pog angle.

24. The method of claim 21 wherein the patient has an increased G-Sn-Pog angle for a period of time in the range of about 9 months to about 24 months after the step of administering.

25. The method of claim 21 wherein the patient has an increased G-Sn-Pog angle for at least about 6 months after the step of administering.
26. The method of claim 21 wherein the patient has an increased G-Sn-Pog angle for at least about 9 months after the step of administering.

27. The method of claim 21 wherein the patient has an increased G-Sn-Pog angle for at least about 12 months after the step of administering.

28. The method of claim 21 wherein the patient has an increased G-Sn-Pog angle for at least about 18 months after the step of administering.

29. The method of claim 21 wherein the patient has a G-Sn-Pog angle of about 169° or greater after the step of administering.

30. The method of claim 21 wherein:
   the HA concentration of the composition is about 25 mg/g,
   wherein the HA used for crosslinking the composition is made with about 90% of low molecular weight hyaluronic acid and about 10% of high molecular weight hyaluronic acid;
   wherein the composition has an elastic modulus comprised between about 500 Pa and about 800 Pa at 5Hz
   wherein the composition has a cohesivity between about 60 gmf and 100 gmf
   wherein the composition has an extrusion force between about 8N and about 10N at 13 mm/min using a 1 ml COC syringe and a 27G x 13mm needle.

31. A method of creating or restoring volume to the chin or jaw of a patient, the method comprising injecting a sterile composition, subdermally or supraperiostially, into the chin area or jawline of the patient in need thereof, the composition comprising a crosslinked hyaluronic acid (HA) crosslinked with 1,4-butanediol diglycidyl ether (BDDE);
   wherein the composition has an elastic modulus between about 500 Pa and about 800 Pa at 5Hz;
wherein the composition has a cohesivity between about 60 gmf and 100 gmf.

and

wherein the method adds volume to the chin or jawline of the patient for a period of time in the range of about 9 months to about 24 months after injection of the composition into the chin or jawline of the patient.

32. The method of claim 31 wherein the composition has an extrusion force between about 8N and about 10N at 13 mm/min using a 1 mL COC syringe and a 27G x 13mm needle.

33. The composition of claim 31 wherein the HA has a degree of crosslinking of between about 4% and about 12%.

34. The composition of claim 31 wherein the HA has a degree of crosslinking of about 6%.

35. The composition of claim 31 wherein the HA has a degree of crosslinking of about 8%.

36. The composition of claim 31 wherein the HA has a degree of crosslinking of about 10%.

37. The composition of claim 31 wherein the HA has a degree of crosslinking of about 6.5%.

38. The composition of claim 31 wherein the HA has a degree of crosslinking of about 8.5%.

38. The composition of claim 31 wherein the HA has a degree of crosslinking of about 10.5%.
FIG. 1
G′ = glabella, Sn′ = subnasale, Pog′ = pogonion

FIG. 2
**A. CLASSIFICATION OF SUBJECT MATTER**

INV. A61L27/20 A61L27/52

According to International Patent Classification (IPC) into both national classification and IPC

**B. FIELDS SEARCHED**

Minimum documentation searched (classification system followed by classification symbols)

A61L

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practicable, search terms used)

EPO-Internal, WPI Data

**C. DOCUMENTS CONSIDERED TO BE RELEVANT**

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Further documents are listed in the continuation of Box C. X See patent family annex.

* Special categories of cited documents:

"A": document defining the general state of the art which is not considered to be of particular relevance

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"O": document referring to an oral disclosure, use, exhibition or other means

"P": document published prior to the international filing date but later than the priority date claimed

"T": later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

"X": document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone

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**Date of the actual completion of the international search**

14 October 2015

**Date of mailing of the international search report**

23/10/2015

**Name and mailing address of the ISA**

European Patent Office, P.B. 5818 Patentlaan 2
NL - 2280 HV Rijswijk
Tel.: (+31-70) 340-2040,
Fax: (+31-70) 340-3016

**Authorized officer**

Heck, Georg
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