Collagen Injectables for Aesthetic and Regenerative Medicine Applications

Subjects: Health Care Sciences & Services

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Soft tissues diseases significantly affect patients quality of life and usually require targeted, costly and sometimes constant interventions. With the average lifetime increase, a proportional increase of age-related soft tissues diseases has been witnessed. Due to this, the last two decades have seen a tremendous demand for minimally invasive one-step resolutive procedures. Intensive scientific and industrial research has led to the recognition of injectable formulations as a new advantageous approach in the management of complex diseases that are challenging to treat with conventional strategies. Among them, collagen-based products are revealed to be one of the most promising among bioactive biomaterials-based formulations. Collagen is the most abundant structural protein of vertebrate connective tissues and, because of its structural and non-structural role, is one of the most widely used multifunctional biomaterials in the health-related sectors, including medical care and cosmetics. Indeed, collagen-based formulations are historically considered as the “gold standard” and from 1981 have been paving the way for the development of a new generation of fillers. A huge number of collagen-based injectable products have been approved worldwide for clinical use and have routinely been introduced in many clinical settings for both aesthetic and regenerative surgery.

Keywords: collagen ; injectable collagen ; medical devices

1. Introduction

Soft tissues loss could be due to iatrogenic, traumatic, pathological, or physiological reasons. Aside from significantly affecting patients’ quality of life, their surgical management requires targeted, costly and sometimes constant interventions. With the average life increase, a proportional increase of age-related soft tissues diseases has been witnessed. Due to this, recent decades have seen a tremendous demand for soft tissue reconstruction strategies and one step resolutive procedures. Intense scientific and industrial research has been conducted to develop innovative approaches or optimize current solutions. Among them, in the last two decades injectable formulations have attracted even more interest for both aesthetic and regenerative surgery for their versatility and multifunctionality (**Figure 1**). Indeed, injectable scaffolds could be used in large and irregularly shaped lesions for a huge variety of damaged tissues, as well as providing temporary pain relief and functional improvement with a single treatment. Thus, injectable formulations could reduce the number of surgical procedures, costs, times and accelerate healing rate and quality.

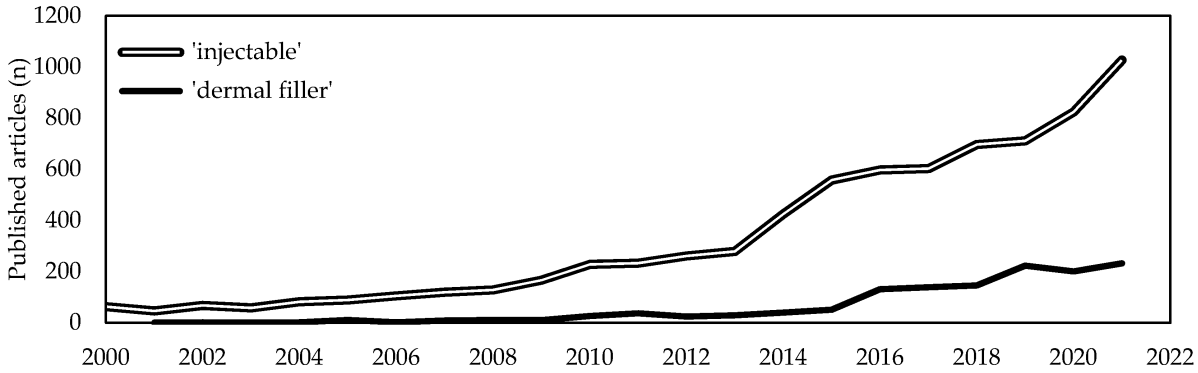

Figure 1. The increasing research interest in injectable formulations and dermal filler. Articles indexed in Scopus (www.scopus.com) with the keywords ‘injectable’ and ‘dermal filler’ and published from 2000 to 2022 (last accessed on 27 May 2022).

The popularity of minimally invasive techniques increased rapidly for several reasons. A principal factor is the acceptance of soft tissue fillers among patients that are not ready for permanent treatments [1]. In the case of patients not wishing to undergo surgery, an easier procedure would generally be more accepted. Moreover, compared to undergoing more

invasive surgery, fillers offer the patient less discomfort and a shorter recovery time, making them very practical in the resolution of minor-serious disease and allowing patients to return immediately to their daily routine [1][2]. Minimally invasive therapies would give a better quality of life also for that part of population that would otherwise not survive the trauma induced by conventional surgeries. Moreover, they could delay the execution of invasive surgical procedures for the implantation of permanent devices [3]. In the case of a staged surgical intervention, the use of injectable systems may avoid the need for multiple invasive operations, thus reducing the related morbidities and negative aesthetic effects associated with repeated procedures [4]. With regard to aesthetic treatments, minimally invasive therapies are preferred as they are less impacting and give a more natural look. Moreover, the lack of an external incision or an autologous tissue donor site is preferred because the absence of scarring is usually socially and psychologically more accepted.

From the surgeon's point of view, the advantages of minimally invasive procedures include principally the need for fewer resources (e.g., operating room, staff, equipment, and time). Being simpler, transcutaneous injections require less operating room staff and time. The pro-regenerative action of injectables would reduce operating room time also because they would be able to restore physiological conditions with a single injection. However, it should not be forgotten that simpler procedures are not less exhausting and do not require less experience. Like any surgical procedure, minimally invasive therapies require adequate knowledge in order to reach the best outcome and avoid unwanted adverse events.

Thus, not only clinicians' but especially patients' preference for fewer invasive and expensive procedures has undoubtedly promoted their use [4][5][6][7][8][9][10]. An injectable formulation for soft tissues reconstruction currently relies on two main approaches, involving autologous tissue displacement (e.g., lipofilling, platelet-rich plasma) or biomaterials-based filling [5]. Both approaches have some advantages and drawbacks. Autologous materials provide the most physiological solution (no adverse events or immune reactions) but suffer from donor site morbidity, volume resorption rate variability, and double surgery requirements. Moreover, their harvesting is a time-consuming procedure that requires double intervention. Alternatively, biomaterials offer an off-the-shelf solution with immediate results and should be distinguished as non-resorbable and resorbable, depending on their half-life. Non-resorbable solutions (e.g., silicone, poly(methyl methacrylate), polyvinylpyrrolidone, polyacrylamide), are permanent (last more than 2 years) but usually suffer from mild-severe adverse reactions (i.e., granuloma, implant encapsulation, persistent pain or rejection) that limit patient satisfaction and could require implant removal surgery [6][7][8][9][10][11][12]. Contrarily, resorbable formulations are usually based on natural biomaterials (i.e., collagen, hyaluronic acid, calcium hydroxyl apatite) and last 6–18 months [13][14][15][16]. Their durability depends on many factors such as the raw material type, product cross-linking degree, lost tissue extension, disease site and etiology, and patient metabolism, age and co-morbidities. The most used resorbable dermal fillers are collagen or hyaluronic acid based.

Collagen is the most abundant structural protein of vertebrate connective tissues [17][18][19][20][21][22][23][24][25] and plays a crucial structural role for the maintenance of tissues' architecture, shape and mechanical properties [20]. Moreover, by mediating a fundamental inter- and intracellular signaling it dictates specialized regulatory functions, especially during development and repair processes [26][27][28][29][30][31][32]. Type I collagen is one of the most widely used biomaterials in the health-related sectors, including medical care and cosmetics [17][18][19][20][21][22][23][24][25][33]. Several collagen-based injectable products have been approved for clinical use and used in many clinical settings.

2. Collagen as Biomaterial

Collagen is the most abundant structural protein of vertebrate connective tissues, and accounts for about the 30% of the total body protein content [17][18][19][20][21][22][23][24][25]. The collagen family is a group of proteins that share a unique molecular fingerprint that is characterized by the presence of a right-handed triple-helical domain formed by three left-handed polyproline-II helices [26][34][35]. This superfamily accounts for 28 members, named from type I to XXVIII according to the discovery order [34][36]. Type I collagen was the first to be discovered and accounts for the 70% of the total collagen found in the human body [26]. This protein is a hetero trimer of about 400 kDa consisting of two identical α1 (≈139 kDa) chains and one α2 (≈129 kDa) chain of about 1000 amino acid residues [20][37]. Both chains are characterized by the repetition of the Glycine-X-Y triplet, where the X and Y positions are usually represented by proline and hydroxyproline, respectively [34][37]. Hydroxylation of proline residues is a typical modification of collagen and, because it accounts for about 11–14% of total residues, it is commonly used as a marker to detect and quantify collagen in tissues [35][38]. Another peculiarity of fibril-forming type I collagen molecules is their ability to spontaneously assemble to form fibrils in which molecules are quasi-hexagonally packed and super-twisted in a right-handed structure along the longitudinal axis of the fibril [39][40][41]. Thus, collagen molecules are aligned parallel to one another with a staggering of about 67 nm (D-banding) and can assemble into fibrils that can be greater than 500 µm in length and 500 nm in diameter [25][34][42][43]. Then, fibrils assemble in fibers whose 3D arrangement is tissue specific.

Type I collagen not only covers a crucial structural role in tissue architecture maintenance but is actively involved in several biological and pathological processes [44]. The involvement of collagen in numerous cellular processes prompted research towards the use of collagen as biomaterial for the development of simplified ECM-like structures [20][35]. To this, several companies isolate medical-grade type I collagen from several sources and manufacture collagen-based implantable devices that are currently used in many clinical settings. Besides its advantages in term of biocompatibility for its physiological structural and non-structural functions, the use of collagen as biomaterial offers several advantages including low immunogenicity, tunable properties, and biodegradability. The low evolutionary gap and the high conservation of type I collagen amino acid composition among vertebrates make that homology up to 95% [19][45][46][47][48].

3. Collagen-Based Injectable Formulations

More than 60 kinds of collagen-based fillers are available on the market, according to the end-use and they have routinely been introduced in many clinical settings (**Table 1**). The most common collagen extraction sources for the manufacture of collagen based injectable formulations are bovine, swine, porcine, equine and human derived, whose advantages and disadvantages are described in depth elsewhere [19][20][25]. Bovine collagen is one of the most commonly used fillers for effectively reducing wrinkles and other facial imperfections. More famous branded bovine-based collagen fillers are Zyderm®, Zyplast®, Contigen® (Allergan Inc., Dublin, Ireland), Artefill® (Suneva Medical, San Diego, CA, USA), and Artecoll® (Canderm Pharma Inc., Saint-Laurent, QB, Canada). Others include CHondroGrid® (Bioteck Spa, Arcugnano, Italy), Integra Flowable Wound Matrix® (Integra LifeScience Corp., Princeton, NJ, USA), Resoplast® (Rofil Medical International, Breda, The Netherlands), Atelocell® (KOKEN Co., Ltd., Bunkyo-ku, Tokyo, Japan). However, bovine collagen is known to be exposed to zoonosis (e.g., the foot and mouth disease and the group of the bovine spongiform encephalopathies, among which the most dangerous for humans is the transmissible spongiform encephalopathy) and to trigger allergies (about 2–4% of population) [49][50][51]. In addition to the strict regulation to which all implantable products are subjected, two consecutive negative patient skin tests at 6 and 2 weeks are required before use [51][52]. This sensitivity has been considered generally acceptable for implants for human use and actually bovine collagen is principally used for the treatment of the integumental [6][53][54][55][56][57][58][59][60][61][62][63][64][65][66][67][68][69][70][71][72][73][74] (NCT01060943) and musculoskeletal apparatus [75][76][77][78][79][80][81][82][83][84][85][86][87][88][89][90] and to a minor extent for the gastrointestinal [91][92][93][94][95][96][97][98], urinary [99][100][101][102][103][104] and cardiovascular [105][106][107] systems. Recently, bovine collagen in fibrillar form has been employed as an organ protection system during thermal ablation of hepatic malignancies [108].

Table 1. Summary of clinically available type I collagen-based injectable formulations.

Source	Manufacturer	Product	Additives	Applications	Ref.
Equine	Euroresearch S.r.l. (Milan, Italy) www.euroresearch.it, accessed on 14 February 2023	Nithya	–	Integumental	[109]
		Linerase	–	Integumental	[110][111][112][113][114]
	Nearmedic Italy S.r.l. (Como, Italy) www.salvecoll.com, accessed on 14 February 2023	Salvecoll-E	–	Integumental	[115]
	Bioteck Spa (Arcugnano, Italy) www.bioteck.com, accessed on 14 February 2023	Biocollagen gel	Type III collagen, bone spongy powder	Musculoskeletal	–
		Biocollagen crunch	Type III collagen, bone powder, bone spongy chips	Musculoskeletal	–
		ActivaBone CLX gel	Bone powder, exur, Vitamin C	Musculoskeletal	–
		ActivaBone Injectable Paste	Demineralized bone matrix, bone powder, exur, Vitamin C	Musculoskeletal	–
		ActivaBone modulable paste	Demineralized bone matrix, bone powder, bone cortical and spongy granules, exur, Vitamin C	Musculoskeletal	–
		ActivaBone Crunch	Demineralized bone matrix, bone powder, cortical and spongy chips, exur, Vitamin C	Musculoskeletal	–

Source	Manufacturer	Product	Additives	Applications	Ref.
Bovine	Bioteck Spa (Arcugnano, Italy) www.bioteck.com, accessed on 14 February 2023	CHondroGrid	–	Musculoskeletal	[90]
	Integra LifeScience Corp. (Princeton, NJ, USA) www.integralife.com, accessed on 14 February 2023	Integra Flowable Wound Matrix	Glycosaminoglycans	Integumental	[66]
		Helitene	–	Soft tissues	[108]
	Rofil Medical International (Breda, The Netherlands)	Resoplast	Lidocaine hydrochloride	Integumental	–
	Suneva Medical (San Diego, CA, USA) www.sunevamedical.com, accessed on 14 February 2023	ArteFill	Polymethylmethacrylate, lidocaine	Integumental	[53][55][56][57][58] [59][60][61][62][63]
	Datascope Corp., (Montvale, NJ, USA)	VasoSeal	–	Cardiovascular	[107]
	BioMimetic Therapeutics, LLC (Franklin, TN, USA) www.biomimetics.com, accessed on 14 February 2023	Augment	β-tricalcium phosphate, recombinant human platelet-derived growth factor-BB	Musculoskeletal	[75][77][78][79][80] [81][82][83][84][85] [86][87][88][89]
	KOKEN Co., Ltd. (Bunkyo-ku, Tokyo, Japan) www.kokenmpc.co.jp, accessed on 14 February 2023	Atelocell	Type III collagen	Integumental, gastrointestinal	[64][65][91][92], NCT01060943
	B. Braun (Crissier, Switzerland) www.bbraun.com, accessed on 14 February 2023	Gelofusine	–	Cardiovascular	[105][106]
	Allergan, Inc. (Dublin, Ireland) www.abbvie.it, accessed on 14 February 2023	Zyplast	Glutaraldehyde	Integumental	[6][54][61][67][68] [69][70][73][74][76] [94][95][97][116]
		Zyderm	–	Integumental	[6][61][67][68][71] [72][96][98][116]
		Contigen	glutaraldehyde	Gastrointestinal and genitourinary	[93][100][101][102] [103][104]

Source	Manufacturer	Product	Additives	Applications	Ref.
Swine	GUNA (Milan, Italy) www.guna.com, accessed on 14 February 2023	Dental Skin BioRegulation	Vitamin C, magnesium gluconate, pyridozine chlorhydrate, riboflavin, thiamine chlorhydrate	Skin	[117]
		Dental ATM BioRegulation	Hypericum	Musculoskeletal	[118]
		MD-HIP	Calcium phosphate	Musculoskeletal	[119]
		MD-ISCHIAL	Rhododendron	Musculoskeletal	[120]
		MD-KNEE	Arnica	Musculoskeletal	[121][122][123]
		MD-LUMBAR	Hamemelis	Musculoskeletal	[120][124][125]
		MD-NECK	Silicio	Musculoskeletal	–
		MD-SHOULDERS	Iris	Musculoskeletal	[126][127]
		MD-SMALL JOINTS	Viola	Musculoskeletal	–
		MD-THORACIC	Cimifuga	Musculoskeletal	–
		MD-MATRIX	Citric acid, nicotinamide	Soft tissues	[125][128][129]
		MD-MUSCLE	Hypericum	Musculoskeletal	[118][120][121][124][125][127][128][129][130]
		MD-POLY	Drosera	Musculoskeletal	–
		MD-NEURAL	Citrullus	Musculoskeletal	[120][124][129]
		MD-TISSUE	Ascorbic acid, magnesium gluconate, pyridoxine chlorhydrate, riboflavin, thiamine chlorhydrate	Soft tissues	–
	Joint Biomaterials S.r.l. (Mestre, Italy) www.joint-biomateriali.it, accessed on 14 February 2023	CartiRegen	Fibrin glue	Musculoskeletal	–
	Ubiosis (Gyeonggi-do, Republic of Korea) www.ubiosis.com, accessed on 14 February 2023	COLTRIX CartiRegen	–	Musculoskeletal	–
		COLTRIX TendoRegen	–	Musculoskeletal	–
	Sewon Cellontech Co., Ltd. (Seoul, Republic of Korea) www.swcell.com, accessed on 14 February 2023	CartiFill	Glucose, CaCl, amino acids, vitamin B, fibrin glue	Musculoskeletal	[131][132], NCT02539030, NCT02519881
		CartiZol	Glucose, CaCl, amino acids, vitamin B	Musculoskeletal	[133], NCT02539095
		RegenSeal	–	Musculoskeletal	[134]
		TheraFill	–	Integumental	[64][65]
	Sunmax Biotechnology Co., Ltd. (Tainan, Taiwan) www.sunmaxbiotech.com, accessed on 14 February 2023	Facial Gain	Lidocaine	Integumental	NCT03844529
		Collagen Implant I	–	Integumental	–
	Evolence (Skillman, NJ, USA)	Dermicol-P35	Ribose	Integumental	[2][135][136][137], NCT00929071, NCT00891774
	Mentor Corp. (Santa Barbara, CA, USA)	Fibrel	–	Integumental	[138][139]

Source	Manufacturer	Product	Additives	Applications	Ref.
Human	Tissue Science Labs. (Aldershot, UK)	Permacol	–	Gastrointestinal	[140][141][142][143][144][145][146]
	EternoGen, LLC (Columbia, MO, USA)	RPC Pure Collagen	Ethylenediamine tetraacetic acid	Integumental	[147]
	Aspid S.A. de C.V. (Mexico City, Mexico) www.aspidpharma.com, accessed on 14 February 2023	Fibroquel	Polyvinylpyrrolidone	Musculoskeletal	[148][149], NCT04517162
	ColBar LifeScience Ltd. (Tel Aviv, Israel) www.ortho-dermatologics.com, accessed on 14 February 2023	Evolence	Ribose	Integumental	[135][150]
	Fascia Biosystem (Beverly Hills, CA, USA)	Fascian	Lidocain	Integumental	[6][151][152]
	Fibrocell Science (Exton, PA, USA) www.fibrocell.com, accessed on 14 February 2023	Isolagen therapy	–	Integumental	NCT00655356
	Inamed Corporation (Santa Barbara, CA, USA) www.inamed-cro.com, accessed on 14 February 2023	Cosmoplast	Glutaraldehyde, lidocaine hydrochloride	Integumental	[6][153]
		Cosmoderm	lidocaine hydrochloride	Integumental	[6][153]
	Life Cell Corp. (Branchburg, NJ, USA)	Dermalogen	Type and VI collagen, elastin, fibronectin, chondroitin sulfate, and other proteoglycans	Integumental	[154]
		Cymetra	Elascin, glycosaminoglycans, Lidocaine hydrochloride	Integumental	[6][96][155][156][157][158]
	Collagenesis, Inc., (Beverly, MA, USA)	Autologen	Elastin, fibronectin, glycosaminoglycans	Integumental	–
		Dermologen	-	Integumental	[156]
Plant	Vesco Pharmaceutical Co. Ltd. (Bangkok, Thailand) www.vescopharma.com, accessed on 14 February 2023	Collagen C 1000	Vitamin C	Integumental	–
Silkworm	Monodermà (Milan, Italy) www.monoderma.com	Fillagen	Hyaluronic acid, carboxymethylcellulose	Integumental	[159]
n. d.	Taumed (Rome, Italy) www.taumed.it, accessed on 14 February 2023	Karisma	Hyaluronic acid, carboxymethylcellulose	Integumental	–
n. d.	LABO International S.r.l. (Padova, Italy) www.labosuisse.com, accessed on 14 February 2023	Fillerina con 3D collagen	Hyaluronic acid	Integumental	–
n. d.	Hebey Mepha Pharm Group Co., Ltd. (Shandong, Hebei, China) www.mephacn.com, accessed on 14 February 2023	Collagen Plus	–	Integumental	–
n. d.	Pierre Mulot Laboratories (Paris, France)	Neutroskin	Vitamin C	Integumental	–

Source	Manufacturer	Product	Additives	Applications	Ref.
n. d.	Elements Pharmaceuticals (Shijiazhuang, Hebei, China) www.elementspharma.com, accessed on 14 February 2023	Ele-collagen	Vitamin C, Vitamin B6	Integumental	–
n. d.	Globus Medical (Audubon, PA, USA) www.globusmedical.com, accessed on 14 February 2023	Kinex Bioactive gel	Bioglass, hyaluronic acid	Musculoskeletal	–

4. Clinical Efficacy of Collagen-Based Injectable Implants

Collagen-based formulations are mainly used for the treatment of several kind of diseases belonging mainly to the musculoskeletal (i.e., hip or knee osteoarthritis [90][119][121][123][133][160][161], sprained knee pain [122], injured cartilage [131][134], piriformis syndrome [128], ankle and hindfoot arthritis [81] or fusion [78][84][85][86][87], lumbar spinal fusion [77], myofascial pain syndrome [118][130], chronic pain [120], acute lumbar spine pain [124], partial-thickness rotator cuff tears [127][134][162], plantar fasciitis [163], calcific supraspinatus tendinitis [126], pain [118][120][124][130]), urogenital (i.e., urinary incontinence [101][103][104][164][165][166][167][168], neurogenic urinary incontinence [169], lichens sclerosus [111], intrinsic sphincter deficiency [170][171][172], post-prostatectomy incontinence [99][102][173][174][175][176], retrograde ejaculation [177]), gastrointestinal (i.e., glottic insufficiency [91][92][94][96][97][156][178][179][180][181][182], rectal fistula [140][141][143][144], fecal incontinence [93][142][183][184]), and integumental (i.e., nasolabial folds [2][54][64][65][74][109][137][147][155][185][186][187][188], nasojugal folds [150], lip [2][55][73][136][153][155], cheek and temple area [155], glabellar groove [55], post-rhinoplasty dorsal irregularities [55][189], depressed acne scars [55][155][190] augmentation, post-burn hands malfunction [66] and vitiligo [110]) systems, as well as for non standard clinical applications (i.e., facial nerve rehabilitation after palsy [129][191], organ protection during thermal ablation [108], COVID-19 associated hyperinflammation [148][149] (NCT04517162), vitiligo [110], ovarian function after premature ovarian failure [192], the closure of artery aneurysms [107][193] and blood volume augmentation [106][194]) (**Figure 2**).

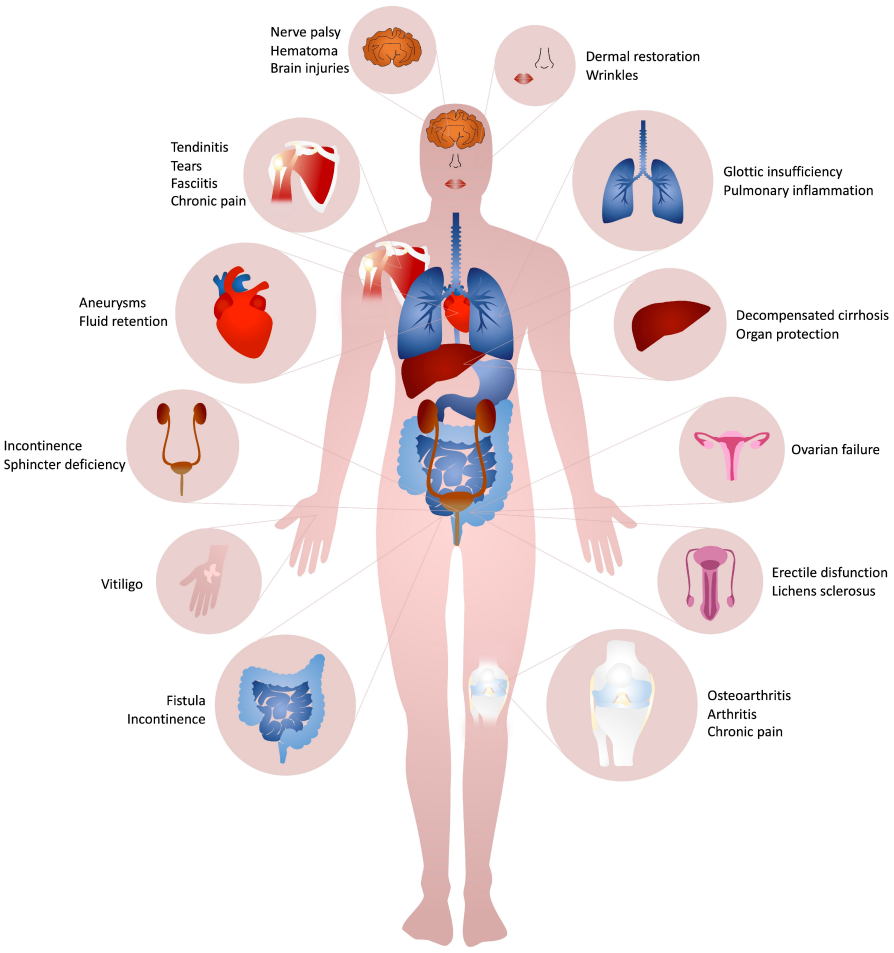

Figure 2. Main collagen-based injectables applications for the treatment of several kind of diseases belonging to the integumental, musculoskeletal, urogenital, gastro-intestinal apparatus, besides for non-standard clinical applications.

4.1. Integumental Apparatus

Type I collagen is the main component of skin (85–90% type I collagen, 10–15% type III collagen). Fibrillar collagen types I, III, and V self-assemble into larger collagen fibers that form the dermis 3D network [195].

To improve the appearance of aged skin many non-invasive (i.e., topical formulations, oral supplements), minimally invasive (i.e., dermal fillers) and surgical treatments (i.e., blepharoplasty) were developed. Although a multitude of topical treatments are available for the improvement of aged skin appearance, these procedures appeared to have minimal ability to remodel dermal ECM [195]. However, collagen supplements originating from various animal sources such as marine, bovine, and porcine were revealed to be able to partially improve skin integrity. Thus, injectables became more popular for their immediate effect. As previously noted, several biomaterials (i.e., collagen, hyaluronic acid, calcium hydroxyl apatite, carboxy methyl cellulose, poly (methyl methacrylate), poly(L-lactic acid) were employed for the development of skin filler, each of which has some advantages and drawbacks.

Among them, collagen is the most promising for its low adverse effects rate and natural filling effect. The return to favor of collagen injectables for aesthetic medicine could be due to the acquired knowledge about chronological skin aging processes. Wrinkles formation is caused by collagen density decrease due to its turn-over slowing-down [195]. Its decreased synthesis and replacement rate causes matrix loss and thus skin collapse and loss of elasticity, which in turn leads to the appearance of wrinkles, folds, and facial contour changes, as masterfully described by Fisher et al. 2008 [195]. Due to this, several commercial collagen-based products are available and are used principally for facial contouring, such as for nasolabial folds [2][54][64][65][74][109][137][147][155][185][186][187][188], nasojugal folds [150], lip [2][55][73][136][153][155], cheek and temple area [155], glabellar groove [55], post-rhinoplasty dorsal irregularities [55][189], depressed acne scars [55][155][190], augmentation [74][155].

4.2. Musculoskeletal Apparatus

Aging leads not only to skin texture loss but also to a progressive and gradual reduction of all human capabilities. The loss of muscle or osteochondral mass with advancing age is the major public health problem for the elderly population. Thus, musculoskeletal apparatus-related medical treatments and costs increase with population age (numbers over 50 years). Among invasive and non-invasive currently available treatments, collagen injections are revealed to be quite effective for the treatment of several musculoskeletal diseases such as hip [119] or knee osteoarthritis [90][121][123][133][160][161], sprained knee pain [122], injured cartilage [131][134], piriformis syndrome [124], ankle and hindfoot arthritis [81] or fusion [78][84][85][86][87], lumbar spinal fusion [77], myofascial pain syndrome [118][130], chronic pain [120], acute lumbar spine pain [124] and in partial-thickness rotator cuff tears [123][134][162], plantar fasciitis [163], and calcific supraspinatus tendinitis [126] and pain [118][120][124][130].

Osteoarthritis is an inflammatory degenerative disease characterized by the progressive damage of articular cartilage and underlying bone that predominantly affects hip and knee [196]. Interleukin (IL)-1β, tumor necrosis factor (TNF)-α, and IL-6 seem to be the main proinflammatory cytokines involved in the pathophysiology of osteoarthritis, even though others, including IL-15, IL-18, IL-21, leukemia inhibitory factor (LIF), and chemokines are implicated [161][197]. The expression of these inflammation mediators in turn activates the cartilage-degrading enzymes, that are matrix metalloproteinases (MMPs) and A disintegrin metalloproteinase with thrombospondin motifs (ADAMTS) [90][197], that progressively degrade the ECM, including collagen. From this observation, several studies were performed to prove the hypothesis that an exogenous administration of collagen may be beneficial to osteoarthritis damaged cartilage and bone.

4.3. Urogenital System

Collagen injections have been revealed to be a minimally invasive and quite effective solution for specific urogenital system diseases such as stress urinary incontinence [101][103][104][164][165][166][167][168], neurogenic urinary incontinence [169], lichens sclerosus [111], intrinsic sphincter deficiency [170][171][172], post-prostatectomy incontinence [99][102][173][174][175][176], retrograde ejaculation [177] and ovarian function after premature ovarian failure [192].

Stress urinary incontinence affects 10–30% of women above 50 years of age [164]. To solve this common issue, in addition to surgical practices (i.e., retropubic bladder neck suspension or slings), biomaterials injections (i.e., teflon, fat, silicone, collagen) have been performed to increase urethral strength and avoid urinary leak. Among them, collagen (Contigen®, Linerase®) has remained the most promising. In a study of Martins et al., either cure or improvement was achieved in 86% of women, with a registered leak pressure increase and reduction in urinary protector use and urine leakage volume [164]. In another study, 48% were totally dry and 31% were socially continent after 2 months [166]. However, because of collagen absorption, stress urinary incontinence recurrence occurred in 41% of patients who achieved continence after 7–8 months

[166]. Collagen reportedly degraded completely within 10–19 weeks, although magnetic resonance imaging of the urethra showed the persistence of the implant for as long as 22 months after injection [175]. Thus, repeated injections (2–5) may be necessary [166][167][169]. Hence, reinjections were performed, with a 42% regain of continence, giving a long-term success rate of 58–60% [166]. Totally favorable results, including improvement (40%) and cure (30%), were also recorded for up to 4 years [103]. However, it should be mentioned that elderly patients should be counseled that approximately 40% will experience recurrent leakage, which may not resolve with reinjection [166]. Conversely, Gorton et al. reported the absence of correlation between long-term success and the number of previous operations, body mass index, age, number or total volume of collagen injections [104].

4.4. Gastrointestinal Apparatus

Injectable collagen has been shown to be effective in the management of gastrointestinal apparatus diseases such as glottic insufficiency [91][92][94][95][96][97][156][178][179][180][181][182], rectal fistula [140][141][143][144] and fecal incontinence [93][142][184].

Glottic dysfunctions due to glottic gap, atrophy, paresis, bowing, paralysis and scarring result in voice absence or alteration. The gold standard for the treatment of vocal fold disfunctions is represented by medialization laryngoplasty or arytenoid adduction, surgical treatments that could significantly improve glottal adduction and phonation. Recently, to reach a better postoperative voice in the long term, biomaterials injection (i.e., autologous fat, silicone, collagen, hyaluronic acid, carboxymethylcellulose) [94][198][199] has been additionally performed. However, autograft represent the known advantages of a double surgery, but means double surgery time and costs. Instead, xenografts are an attractive alternative for supplementing arytenoid adduction, because of their noninvasiveness, ready availability, and possibility to be performed under local anesthesia. Among them, collagen injectable formulations proved to be effective for vocal fold management. Patients treated with 1–2 mL of selected collagen injectable formulations (Koken®, AlloDerm®, Zyplast®) showed at least some improvement in vocal function after the treatment, according to the Grade, Roughness, Breathiness, Asthenia, Strain (GRBAS) scale, Maximum phonation time, Mean flow rate, Relative glottal area. In particular, perceptual and objective voice quality improvement (less weak and breathy) was registered, with an increase of the mean maximum phonation time from around 8–11 s to 13–15 s, and a reduction of the mean flow rate from 322–564 mL/s to 223–385 mL/s and of the glottal gap [91][92][179], for at least up to 2 years after operation [92]. Thus, from the moment in which the safety and efficacy of collagen injections for the treatment of the vocal cords was affirmed by Ford and Bless in 1993 [181], the injection of heterologous material started to be even more required, given the positive feedback and long-term results [96]. Although collagen injections were quite effective, and serious adverse events were rare [91][92][95][181], documented complications included local abscess, migration of the implant, hypersensitivity reactions, stiffening, fusiform collagen mass, nodules [94][156] principally related to the procedure and injection site [91]. Indeed, if properly injected, the complication rate after collagen injection would decrease [179].

5. Adverse Reactions to Collagen-Based Injectable Implants

All types of fillers may trigger an early tissue response to the injected material. Regardless of the filler material, frequently reported side effects are bruising, redness, swelling, induration, erythema pain, tenderness, itching and, in the most severe cases, violaceous plaque and granulomas [200][201][202]. These side effects are usually mild and transient and resolve spontaneously after a short time. Only a few cases of severe and permanent complications have been registered.

Although compared with other injectables collagen-based formulations have many advantages, it does not mean that they are absolutely safe. Indeed, severe and non-severe adverse reactions to collagen treatments may occur. To the best of our knowledge, based on harvested and available data on adverse reactions registered after collagen-based commercial product applications, severe adverse events accounted for 8.2% (211 cases on 2587 patients), while mild adverse events accounted for about 5.3% (137 cases on 2587 patients) of those receiving the treatment.

With a focus on collagen extraction sources, it emerged that severe adverse events accounted for 12.1% (211 cases on 1742 patients) and mild events for 3.8% (67 on 1742 patients) when bovine collagen was used. In particular, severe adverse events were addressed to the use of one collagen-based product that was Augment®, an injectable formulation composed of bovine collagen, β-tricalcium phosphate and recombinant human platelet-derived growth factor-BB [80] (NCT01305356, NCT00583375). Leaving aside the Augment® severe adverse reactions (211 on 1742 procedures), the other analyzed bovine collagen-based products (i.e., ChondroGrid, Atelocell, Zyderm, Zyplast, Contigen, Gelofusine, Flowable wound matrix and Helitene) were not associated with such issues [66][91][92][94][96][106][108][160][166][167][169][194][203] (NCT02808325, NCT04637308, NCT02715466, NCT01515397, NCT02631356, NCT00868062). Since bovine collagen

appeared to be safe, these events could be ascribable to other Augment components, without certainty. As regards mild adverse reactions, they were registered only when using Augment, Chondrogrid or Zyderm [79][84][96][160].

Porcine derived collagen-based products (i.e., Cartifil, Cartizol, Fibroquel, Permacol and MD products) revealed to not trigger severe adverse events (no cases on 751 procedures) and to be responsible for the 9.2% of mild adverse events (69 cases on 751 procedures) [119][120][121][122][124][125][126][127][128][129][131][133][134][140][141][142][143][144][148][149][161][184] (NCT02539030, NCT02539095, NCT04019782, NCT03323567, NCT02539082, NCT01528995, NCT04517162, NCT04353908). Mild adverse events could be due both to collagen type or to other components (i.e., glucose, CaCl, amino acids, vitamin B, fibrin glue for Cartifil/Cartizol; polyvinylpyrrolidone for Fibroquel) or to the injection procedure. However, data were not enough to identify the causes. Definitely though, the low mild adverse events rate of the MD product could be clearly ascribable to the presence of other bioactive compounds (such as calcium phosphate, rhododendron, arnica, hamemelis, silicon, iris, viola, cimifuga, citric acid, nicotinamide, hypericum, drosera, citrullus, ascorbic acid, magnesium gluconate, pyridoxine chlorhydrate, riboflavin, thiamine chlorhydrate) that had a strong impact on patients' post intervention events. As regards Permacol, since it is not characterized by the presence of other components, adverse events triggered by its use could be attributed to collagen type, to the injection procedure, to the disease or to the patient specific response. In this case, available data do not allow clearly attribution of responsibility. However, mild adverse event usually resolved spontaneously or required minimal, not invasive intervention [119][129][133][134][143][149][184] (NCT04353908, NCT04517162, NCT01528995, NCT02539030).

The third most used collagen type Is equine derived collagen, whose use is very recent and thus limited compared to bovine and porcine derived injectable products. Indeed, it has been reported to be used (i.e., Linerase, Savecoll-E) only on 94 patients, with no adverse events and only one registered mild reaction (1.1%) [110][111][112][115]. Thus, although this percentage seems to be very low compared to other products, the limited number of executed procedures with equine collagen prevented the assessment of this collagen type as safer. This consideration could be applied also for human collagen derived products (i.e., Cymetra, Dermologen) for which two severe and zero mild adverse events were registered on the only patients [156][181]. However, these data and these considerations are only indicative because not all studies reported participant number and adverse event occurrence.

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