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Exploring the Neo-Collagenesis Mechanism of Calcium Hydroxylapatite: A Comprehensive Literature Review

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Abstract: ***Calcium Hydroxylapatite CaHA has emerged as a pivotal biostimulator filler in aesthetic medicine, renowned for its dual action of immediate soft tissue augmentation and stimulation of collagen production over time. This literature review delves into the neo - collagenesis mechanism of CaHA, exploring its application, effectiveness, and the underlying biological processes. By analyzing various theories and articles, this review illuminates CaHAs role as a minimally invasive dermal filler in combating signs of skin aging and promoting regenerative effects on the skin. The review underscores the necessity for future research, advocating for higher quality clinical studies with larger sample sizes to unravel the intricacies of CaHAs action mechanisms further. This comprehensive insight aims to contribute to the understanding and optimization of CaHA use in regenerative aesthetic treatments, highlighting its significance in halting the aging process through enhanced collagen production and gene expression modulation.***

Keywords: Calcium Hydroxylapatite, Dermal Filler, Skin Aging, Aesthetic Medicine

1. Introduction

Aesthetic medicine has made great progress in the last decade in terms of our understanding of facial reconstruction and the cumulative effects of the aging process, and how dermal fillers can be used to repair, reduce, and even reverse these changes. Initially, aesthetic practitioners pursued lines and wrinkles, based on experience with bovine collagen injections beginning in the early 1980s. Calcium Hydroxylapatite (CaHA) is a dermal filler commonly used in aesthetic medicine to add volume and contour. Understanding the mechanism of action of CaHA may help improve our understanding of its clinical applications. The demand for skin rejuvenation procedures which are minimally invasive procedures to address the loss of youthful appearance and age - related signs of aging such as skin wrinkling, deep wrinkles and bone resorption, especially on the face, is increasing. Calcium Hydroxylapatite (CaHA) is a minimally invasive dermal filler commonly used to correct certain signs of skin aging, providing “real - time” results with good results and high patient satisfaction scores. Additionally, evidence suggests that CaHA generally has a good safety profile (Kadouch, 2017).

Calcium Hydroxylapatite CaHA is one of the most widely used fillers throughout the world. Calcium hydroxylapatite has been widely used to reduce moderate to severe facial lines and folds. Calcium hydroxylapatite is a natural substance found in bones. Just like hyaluronic acid, this filler is also soft like gel but thicker. This means that Calcium hydroxylapatite filler can last longer than hyaluronic acid filler. Calcium hydroxylapatite usually lasts 12 months. Not only does it reduce wrinkles and increase volume, calcium hydroxylapatite also helps stimulate natural collagen production, which can make the face firmer (He, 2017). Calcium hydroxylapatite (CaHA) Merz Pharmaceuticals GmbH, Frankfurt, Germany) is a unique product because it provides volume replacement and collagen bio - stimulation as the primary MOA. In addition, CaHA is biodegradable and is reabsorbed naturally by the host's metabolic processes. This MOA of biostimulator, with the highest reabsorption, results in a unique performance profile for CaHA. CaHA is a highly effective agent for many areas of facial soft tissue augmentation and is associated with an established safety profile.2013 marks a decade of CaHA technology, which first received European Union approval in 2003 for plastic and reconstructive surgery, including deep dermal and subdermal soft tissue augmentation of the facial area. In subsequent years, the scope of use of CaHA has expanded along with developments in the field of aesthetic medicine, from a two - dimensional, surface - oriented approach, which concentrates on eliminating facial lines and folds, to a three - dimensional approach that also addresses both. loss of soft and hard tissue volume on the face and hands (Zarbafian, 2022).

Calcium hydroxylapatite as a biostimulator filler that provides immediate soft tissue enlargement and stimulates collagen production over time. CaHA can be injected into the deep dermis, subcutaneous or supraperiosteal tissue, and can be diluted in various concentrations providing exceptional product versatility. Its high viscosity limits product migration, and its high cohesiveness enables high lifting capacity. It is also elastic and resistant to deformation under stress. CaHa can be injected with a blunt needle or cannula, and the technique varies by area and treatment plan. It is contraindicated in areas of hypermobility with thin skin such as the lips, in the perioral and periorbital areas where there is an increased risk of nodule formation, and in the glabellar area and on the nose due to the risk of vascular occlusion (Couderot, 2016).

The purpose of this literature review is to elucidate the neo - collagenesis mechanism of Calcium Hydroxylapatite CaHA in aesthetic medicine, assessing its efficacy as a dermal filler and its broader implications for regenerative treatments.

2. Method

The methodology of this article, a literature review, involves an in - depth examination of theories, findings, and various

research sources. These references form the basis for reviewing both clinical and theoretical findings.

3. Results

Calcium Hydroxylapatite relationship with MMP - 1

Matrix metalloproteinase - 1 (English: vertebrate collagenase; interstitial collagenase, fibroblast collagenase, matrix metalloproteinase 1, MMP - 1, EC 3.4.24.7) is a collagenase enzyme in vertebrates with the MMP - 1 genetic file which plays a role in the degradation of collagen types I, II, and III which is found in the interstitium and α - macroglobulin, with a Zn cofactor. The triple collagen chain will be cut approximately 3/4 of the length of the polymer molecule, from the N terminus at 775 - Gly - | - Ile - 775 (Casabona, 2017). MMP - 1 is synthesized and released in the form of an inactive proenzyme with an estimated molecular weight of 55 kD. ECM and functions to break down collagen located in keratinocytes dependent on zinc and calcium produced and released from skin fibroblasts and endopeptidase67, MMP - 1 is activated through proteolytic cleavage, resulting in the release of the active form of MMP - 1 with an estimated molecular weight of 24 kD. In cultured fibroblasts or skin tissue equivalent models, both active and inactive MMP - 1 accumulate in the culture medium (Fan, 2019).

Calcium Hydroxylapatite with Type 1 Collagen

Collagen is a type of protein formed from amino acids. Collagen is hard and difficult to dissolve in water. Collagen is what makes up one third of the protein in the human body. Not only that, it turns out that collagen is spread throughout the human body and is a protein that forms or builds several parts of the body. In the human body, especially the skin, there are layers of skin. In this layer of skin there are special cells that can produce pro - collagen in a tiny molecular form. These mini or pro collagen molecules are formed from protein and vitamin C whose nutrients are successfully absorbed by the body (González, 2019). Collagen types I and II are natural polymers widely used in cartilage tissue engineering that present innate biological cues that enable the interaction of chondrocytes with the scaffold, as well as providing the necessary space for tissue growth. This is due to the recognition of collagen by cellular enzymes). Type 1 is a type or type of collagen that plays an important role in forming at least 90% of natural collagen. This type of collagen or type 1 is made from fibers that have a dense texture. Type 1 collagen has a role in providing collagen to the structure of bones, tendons, cartilage, skin, connective tissue in the body and teeth (Baumann, 2021).

Calcium Hydroxylapatite with c - Jun Protein

C - JUN amino acid 1 - 81, is a non - glycosylated polypeptide chain. C - JUN is a maltose - binding protein (MBP) fusion protein with an amino - terminal poly - histidine tag and was purified by a proprietary chromatographic technique. C - JUN is a gene that, when combined with c Fos, forms the early response transcription factor AP - 1. C - JUN is activated by the JNK pathway. C - JUN is a gene suspected of transforming avian sarcoma virus 17. C - JUN is a protein that is very similar to viral proteins, and interacts directly with specific target DNA sequences to regulate gene expression. The JUN C gene is nonnuclear and maps to 1p32 - p31, a chromosomal region involved in translocations and deletions in human malignancies. c - Jun N - terminal kinases (JNKs), were initially identified as kinases that bind and phosphorylate c - Jun at Ser - 63 and Ser - 73 in its transcriptional activation domain. They belong to the mitogen - activated protein kinase family, and are responsive to stress stimuli, such as cytokines, ultraviolet irradiation, heat shock, and osmotic shock. They also play a role in T cell differentiation and cellular apoptosis pathways. Activation occurs through double phosphorylation of threonine (Thr) and tyrosine (Tyr) residues in the Thr - Pro - Tyr motif located in the kinase subdomain VIII. Activation is carried out by two MAP kinases, MKK4 and MKK7, and JNK can be inactivated by the protein phosphatases Ser/Thr and Tyr (Casabona, 2017).

The role of transforming growth factor - β (TGF Beta in the aging process

Transforming growth factor - β (TGF - β) is a pleiotropic cytokine that regulates various cellular processes and has important roles in embryonic development, physiological tissue homeostasis, and various pathological conditions. TGF - β exerts potent growth inhibitory activity on a variety of cell types, and various growth regulatory mechanisms have been reported to be associated with cell senescence and stem cell senescence phenotypes in previous studies. TGF - β performs diverse functions by modulating the expression of downstream target genes through transcriptional and post - transcriptional mechanisms as well as protein modulation in a context - dependent manner. Importantly, downstream targets of TGF - β signaling include many regulators involved in various aspects of the aging process, such as cell proliferation, cell cycle regulation, reactive oxygen species (ROS) production, DNA damage repair, telomere regulation, and unfolded protein response. (UPR), and autophagy. Due to the large overlap between these two pathways, TGF - β signaling exhibits multifaceted crosstalk with the aging process. At the cellular level, TGF - β signaling has been shown to play an important role in cellular senescence and stem cell senescence. So TFG - β is related to the aging process and disease (Zerbinati, 2018).

4. Discussion

Skin aging is a common phenomenon in which the skin can no longer maintain normal hair thickness, strength, function and density. By influencing different cell mechanisms, such as collagen synthesis, elastin production and angiogenesis, it is possible to stimulate the regeneration of old tissue, a new concept referred to as regenerative aesthetics (Figueredo, 2022). Several of these mechanisms have been suggested to support CaHA as a regenerative aesthetic treatment. Research has shown that CaHA can cause differentiated cell proliferation, increased collagen and elastin production, and an increase in the number of new blood vessels (Kadouch, 2017). Calcium Hydroxylapatite (CaHA) is a dermal filler commonly used in aesthetic medicine to add volume and shape. Understanding the mechanism of action of CaHA can help improve our understanding of its clinical applications (Zerbinati, 2018).

CaHA can provide skin regenerative effects, including cell proliferation, collagen and elastin synthesis, and stimulation of angiogenesis. Limited data also suggests an anti -

inflammatory effect of CaHA. Cell proliferation is considered a key process of tissue regeneration (Fan, 2019). Migration and proliferation of fibroblasts as well as extracellular matrix synthesis are characteristic of the proliferation phase of the dermal repair process. Fan (2019) explained that although current evidence does not show consistent findings regarding CaHA - stimulated fibroblast proliferation as measured by cell number, our findings suggest that CaHA may influence cell proliferation as reflected by higher Ki - 67 levels; this process is not accompanied by an increase in Lactic Acid Dehydrogenase (LDH) levels, which is an indicator of potential toxicity. These findings suggest that CaHA can stimulate the proliferation of collagen - producing cells, which may partly explain the increase in collagen production. Although the role of Ki - 67 is not fully understood, evidence suggests that Ki - 67 expression influences heterochromatin organization in proliferating cells, thereby controlling gene expression (Sobecki, 2016).

The CaHA mechanism can induce the synthesis of type I and III collagen in the early phase, and then gradually type I collagen replaces type III collagen, consistent with the natural remodeling process. Type I collagen makes up 80–85% of the dermal extracellular matrix in the skin, while type III collagen makes up around 8–11% (Davison, 2019). Both types of collagen are estimated to have a half - life of around 15 years in the skin, indicating their turnover is very slow (Davison, 2019). Collagen production decreases with age, and elderly people show up to 75% less collagen production than younger age groups. Decreased collagen types I and III are characteristic of sun - damaged and chronologically aging skin characterized by morphological and mechanical changes that result in wrinkle formation, loss of elasticity, and dryness (Davison, 2019). Therefore, CaHA can counteract this process by inducing collagen synthesis, and persistent type I collagen synthesis can provide strength and resilience to the skin (Fisher, 2021). Future research is needed to explore different collagen synthesis time intervals and number of CaHA injections required for optimal results. Elastin, the main component of elastic fibers, was shown to increase after CaHA injection. The production of elastic fibers provides stretch, suppleness, and elasticity to the skin, and is an integral part of a youthful appearance (Baumann, 2021).

5. Conclusion

It can be concluded that CaHA can provide a regenerative effect on the skin. Future higher quality clinical studies with larger sample sizes and better statistical approaches, are needed to better understand the mechanisms of action of CaHA such as cell proliferation, collagen synthesis.

6. Suggestion

In the use of aesthetic medicine, regenerative treatments aim to stop the aging process by increasing collagen production, stopping collagen degradation, or by modulating gene expression. So you can pay attention to how to use it.

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