Synergistic therapy for skin aging: The association of the microneedling technique and vitamin C from the point of view of orofacial harmonization

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ABSTRACT

The increase in life expectancy around the world and the need to look good explains the growth in the number of clinical services focused on aesthetics. As it is the most exposed organ, the skin has a strong social concept since skin changes represent a criterion of beauty and greatly affect people's self-esteem. Several clinical manifestations occur in skin aging, such as wrinkles, sagging, roughness, dryness, and blemishes related to both intrinsic and extrinsic factors, especially oxidative radicals induced by ultraviolet light, which contribute to the etiology of aging. Our objective is to discuss the improvement of skin quality when combining the microneedling technique with the use of topical vitamin C.

Keywords: Dry needling, Ascorbic acid, Skin aging, Skin.

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INTRODUCTION

Modern dentistry has long since ceased to be related to the mutilating and extractionist model as it was represented in Brazil decades ago. From this new scenario, new strands have been emerging and, in 2019, the Federal Council of Dentistry (CFO) regulated Orofacial Harmonization (HOF) as a new dental specialty. The ideal of HOF is to study and intervene in attached structures covering the extraoral region, with the aim of harmonizing facial proportions, promoting greater symmetry to the face, valuing specific points and reducing the signs of aging. All of this is associated with the functional and aesthetic understanding of the stomatognathic system (GARBIN et al., 2019).

Through the face we relate directly to the world and it is also where our individual characteristics directly associated with self-esteem and recognition are imprinted. When we perform facial movements, we express emotions and feelings (LINS et al., 2021). However, the physiological aging process induces the loss of subcutaneous fat and dermal collagen, resulting in furrows and depressions in the face, negatively influencing aesthetics (NOVAIS; SOUZA, 2020).

Therefore, over time everyone will age and it is natural that the appearance of facial expression lines become accentuated with progressive age, reinforced by muscle action, volumetric loss of the face and exposure to individual factors such as lifestyle and genetic characteristics. Aging is a process that cannot be reversed and happens gradually and slowly. Aesthetic facial rejuvenation procedures have become increasingly present within clinical care and the explanation for this fact is the increase in life expectancy combined with the appreciation of youth and beauty (LINS et al., 2021).

The search for treatments that prevent and/or reverse skin aging makes facial aesthetics a target for research. Everyone wants to look youthful because aging has an influence on social behavior, psychologically affecting the individual and their self-esteem (FERREIRA et al., 2020).

Skin ages through a multifactorial process induced by intrinsic factors such as metabolic processes and senescence, as well as environmental factors such as smoking, air pollution, and solar radiation – including visible light and exposure to infrared light. Because it is an exposed organ, the skin is very susceptible to extrinsic factors. There are several mechanisms by which UV radiation induces photoaging, including direct DNA damage, cell surface receptor-initiated signaling, mitochondrial damage, and increased production of Reactive Oxygen Species (ROS) and Reactive Nitrogen Species (ERNS). These molecular changes have undesirable aesthetic consequences, including erythema, edema, sunburn, sagging, and reduced skin integrity (MESA-ARANGO et al., 2017).

Vitamin C (VC) or ascorbic acid has an effective role as a reducing agent of the effects of the aging process on the skin and can also be used in dermocosmetic formulations due to its excellent antioxidant property in inhibiting and reducing the formation of free radicals. It is in the periorbital

region (region with less skin thickness) where the first signs of aging appear. VC acts in a relevant way in this region due to its properties of protection and stimulation of the synthesis of collagen and elastin fibers responsible for the support and firmness of the skin. The production of melanin pigments is also affected by VC through the inhibition of the enzyme tyrosinase, the main regulator of pigment formation, and is therefore suggested as a depigmenting agent (COSTA DE OLIVEIRA et al., 2018).

To ease the inevitable path of aging, HOF uses several procedures and techniques developed for the treatment of facial rejuvenation, including microneedling, which is also known as Collagen Inducing Therapy. This is a non-surgical, percutaneous collagen inducer that consists of performing microperforations through small needles on the patient's face for the application of active ingredients that permeate to the epidermis and/or dermis region. The great benefit of microneedling lies in the fact that it stimulates collagen production, allowing the permeation of a greater amount of active ingredients into the skin without causing total removal of the epithelium, which is not observed in other ablative techniques (GARBIN et al., 2019).

Among the active ingredients that can be associated with microneedling therapy, Vitamin C has been indicated to improve and attenuate the signs of aging, as it is a potent antioxidant, protecting the skin from the action of free radicals, stimulating chemical reactions in the metabolism of collagen formation and, consequently, in the formation of new tissue (PEREIRA et al., 2021).

The scope of this study is to analyze the information on the benefits of microneedling associated with the use of Vitamin C, including the mechanism of collagen induction, in view of its use as a therapeutic device in orofacial harmonization.

SOME THEORETICAL FRAMEWORKS

STRUCTURE AND FUNCTIONS OF THE SKIN

The skin is an organ of complex formation and its own structure, which has several tissues, cell types and specialized structures, distributed in interdependent layers. Its origin is embryological from the ectodermal and mesodermal leaflets. From the ectoderm come the epithelial (epidermis, glands, hair and nails) and neural (melanocytes and nerves) structures, while from the mesoderm derive the dermis and hypodermis. The skin area varies from 1.5 to 2.0 m2 in adults and weighs approximately 15% of their body weight, being the largest organ in the human body. It has an appearance, structure, and functions that vary according to the region of the body.

Therefore, the skin is an organ of defense and external covering, with the ability to adapt to variations in the environment and the needs of the organism it protects, covering the body completely. It is multifunctional, playing essential roles for immune homeostasis, sensitivity, protection against external aggressions (chemical, physical or biological), against the loss of water

and proteins to the external environment. It also receives stimuli from the environment and collaborates with mechanisms to regulate its temperature (CESTARI, 2018).

As it is a dynamic structure, the skin presents constant changes, It is equipped with a great capacity for renovation and repair, and a certain degree of impermeability. In the human being, the skin is an organ of great importance, as it aims to maintain a balance with the external environment, in the sense of the vital maintenance of the internal environment. Its most important and vital function is the conservation of homeostasis (thermoregulation, hemodynamic control, and production and excretion of metabolites).

It also fulfills a sensory function, through the elements of the nervous system located in the dermis, and a defense function against physical, chemical and biological aggressions, for which keratinization, the lipid mantle and the immune system stand out due to their importance. The skin and its appendages suffer repercussions with hormonal action because they have receptors for both estrogens and androgens. The hormonal decrease that accompanies age has an effect on the structure and function of the skin and its appendages (AZULAI, 2017).

Anatomically, the skin is composed of three distinct layers, but they work in close relationship, they are: epidermis, dermis and hypodermis. The outermost epidermis and the deepest dermis. The epidermis fulfills most of the skin's barrier functions and is composed predominantly of cells, mainly keratinocytes. Keratinocytes are arranged in four layers throughout the epidermis; which undergo continuous transformations as these cells divide and proliferate away from the basal layer, which is closer to the dermis. From the interior to the surface, these layers are: basal, spinous, granular, and corneal layers (PULLAR et al., 2017).

The differentiation time of a basal cell until it reaches the stratum corneum is approximately 26 to 28 days. This process is called keratinization and involves the production of specialized structural proteins, lipid secretion, and the formation of a cellular envelope of cross-linked proteins. During differentiation, virtually all cell organelles disappear, including the nucleus. The cytoplasm is also removed, although there is evidence that some enzymes remain. These cells are sealed with lipid-rich sectors, forming a barrier impermeable to water. This layer is known as the stratum corneum and serves as the primary barrier of the epidermis, although the lower epidermal layers also contribute (PULLAR et al. 2017).

According to Junqueira (2018), in addition to keratinocytes, the epidermis has three other types of cells: melanocytes, which are cells responsible for the synthesis of melanin, a pigment whose function is to protect against ultraviolet rays; the Langerhans cells which are the cells responsible for activating the system immune acting as macrophages against foreign particles and microorganisms; and the Merkel cells or discs that are present between the epidermis and dermis, attaching to sensory nerve endings and acting as touch or pressure receptors.

Melanocytes are dendritic cells and make up 10% of the cells in the basal cell layer. They secrete melanin, a pigmented polymer that absorbs ultraviolet (UV) radiation from the light spectrum and determines skin color. There is another population of melanocytes in the hair follicle responsible for hair color and replacement Of melanocytes epidermal lesions, when necessary. Melanin is produced and stored by melanosomes, a specialized organelle. Melanin is synthesized from tyrosine, going through several steps that require the share Of enzyme Responsible tyrosine By CATALYZING Of reaction of melanogenesis. Melanosomes healthy Phagocytosed by keratinocytes and transported to a region above the nucleus of the keratinocyte, acting as a protective shield against UV radiation. One melanocyte provides melanosomes for up to 30 to 40 keratinocytes. All humans have the same number of melanocytes, which do not proliferate or migrate under basal conditions, so a specific stimulus must occur, usually UV radiation. The variety in skin color tones stems from variations in melanosomes. Individuals with darker skin have more numerous, larger, and more dispersed melanosomes. Exposure to UV radiation stimulates the secretion of melanin inside the melanosomes and gives the skin a "tanned" tone. Tyrosinase deficiency is associated with albinism, while vitiligo is caused by the absence of melanocytes. (BOHJANEN, 2017).

The skin plays an important role in the metabolism of vitamins**.** The main Sources of vitamin D are made up of the diet, but the skin is extremely important in the production of precursors of this vitamin. On exposure to UV light, the pro-vitamin D3 (7-dihydrocholesterol) in the epidermis is converted into pre-vitamin D which is converted into vitamin D3. Vitamin D3 is converted to its metabolically active form in the liver and kidneys (JUNQUEIRA, 2018). In relation to the dermis, its main components include collagen (70% to 80%), which provides resistance; elastin (1% to 3%), which gives elasticity; and proteoglycans, which constitute the amorphous substance around collagen and elastic fibers; in addition to protein fibers, reticulin fibers, blood vessels, and lymphatics, nerve endings, sensory organs, hair follicles, and sweat and sebaceous glands.

This whole set is surrounded by the fundamental substance, which also contains several cell types such as fibroblasts, macrophages, melanophages, mast cells, leukocytes (such as neutrophils, eosinophils, lymphocytes, monocytes and plasma cells), T lymphocytes and dendritic cells, involved in the skin's immune defense. The fibers and the fundamental substance are manufactured by fibrobroblasts, which are the main cells of the dermis (CESTARI, 2018).

The dermis is structurally organized into compartments: the papillary dermis (superficial), the reticular dermis (deep), and the periadnexal dermis. The papillary dermis follows the basal layer, has thinner connective tissue composed mainly of type III collagen, is highly vascularized and fills the concavities between the epidermal ridges, giving rise to the dermal papillae. In the papillary dermis, collagen and elastic fibers are vertically oriented, and the ground substance is more abundant than in the reticular dermis. The reticular dermis represents 4/5 of the thickness of the dermis, being located

below the level of the epidermal ridges. It consists of thick collagen fibers (mainly type I) intertwined, with a direction parallel to the epidermis, mixed with elastic fibers, arranged parallel to the surface of the skin, gathered with the fundamental substance. The third region, the adventrial (periadnexial) has the same structure as the papillary dermis, surrounded by pilosebaceous follicles, glands and vessels, and is formed by thin bundles of collagen. In the dermis, cutaneous appendages such as sebaceous and sweat glands, hair, and nails are present (BARCAUI et al., 2014).

Between the dermis and the epidermis is present the dermal-epidermal junction, a structure that is a mesh of macromolecules that connects keratinocytes of the basal layer with the collagen fibers (mainly type IV collagen) of the papillary dermis, keeping these two layers correctly anchored, allowing permeability in the exchanges between these two components and acting as a filter for the trafficking of inflammatory or neoplastic materials and cells. It plays the role of a barrier and a filter, which gives it a dual function. As a barrier, it is selective and allows the passage of nutrients from the dermis to the cells of the epidermis. However, in the opposite direction (from the epidermis to the dermis), everything that comes into contact with the epidermis and could pass through it, finds in it a barrier that is difficult to overcome. The cells of the basal layer of the epidermis rest on a structure called the basement membrane. In a simple way, this union is composed of the lower pole of the basement membrane and its hemidesmosomes, lamina lucida, dense lamina and sublamina dense (CESTARI, 2018).

The last and deepest layer of the skin, called the hypodermis (adipose panniculus) is made up of adipocyte lobules bounded by collagen septa with blood vessels, lymphatics and nerves. Classified as an endocrine organ, it has the functions of energy reserve, protection against trauma, thermal insulation, shapes the body and allows the skin to glide easily over the underlying structures (AZULAY et al., 2017; CESTARI, 2018).

SKIN AGING

Aging is a progressive process that involves a reduction in the body's maximum function and reserve capacity. It is the result of both the genetic program and the cumulative environmental effects. The main theories of aging attempt to elucidate the processes determined by genetics as well as the environmental ones responsible for senescence. The process of telomere shortening explains that aging is part of a process inherent to the body. The Telomeres are the terminal portions of chromosomes, which shorten with each cell cycle. As the telomere reaches a critical length, the cell cycle stops and apoptosis occurs. The theory of free radicals, on the other hand, highlights the role and function of extrinsic factors. According to this theory, aging results from the accumulation of cellular damage produced by the excess of reactive oxygen species (ROS) that are generated as a consequence of oxidative metabolism. Age-associated cell damage includes DNA oxidation resulting

in mutations, oxidation of proteins reducing their function, and the oxidation of membrane lipids, affecting transport efficiency and possibly transmembrane signaling. The main source of excess ROS implicated in aging is the generation of mitochondrial oxidative energy (Landau et al., 2007). Costa et al. (2015) explain the generation of free radicals as a physiological activity, performing extremely important biological functions for several biochemical reactions. Among these functions is the generation of a molecule that functions as an energy source for cells, adenosine triphosphate participation in defense mechanisms that occur during an infectious process. However, the formation of free radicals in vivo also happens due to exposure to external factors such as smoking, drugs, and UV rays. Due to aerobic metabolism, oxygen undergoes tetravalent reduction, mainly in the mitochondria, receiving four electrons, as a result water molecules (H2O) are formed. Reactive intermediates such as hydrogen peroxide (H2O2), superoxide (02), hydroperoxyl (HO2) and hydroxyl (OH) are also generated.

Skin aging can be classified into: intrinsic aging (chronological) and extrinsic aging (photoaging). Intrinsic aging is related to genetic and physiological changes, while extrinsic aging is directly linked to external factors, i.e., sun exposure (ultraviolet radiation - UVR), pollution, daily care and all the conditions that contribute to skin wear. The two separate skin aging processes affect the skin at the same time (BARONI et al., 2012).

According to Mesa-Arango et al. (2017), the natural aging of cells (cellular senescence) is the result of physiological factors and genetic predisposition. Aging skin is dry, sagging and atrophic with fine wrinkles and a variety of benign neoplasms. The signs of this process are a drop in hormone levels and cell proliferation, in addition to other factors such as accumulation of dysplastic keratinocytes, degradation of the extracellular matrix, shortening of telomeres, mutations of the genes of cell organelles (nucleus and mitochondria) and various metabolic deformities of amino acids and lipids.

All of these disorders have functional and physical consequences. For example, the dry appearance of the skin is a result of abnormal water distribution or a lack of hygroscopic substances. The decrease in the oxidative activity of the cells leads to an exaggerated production of ROS in the mitochondria, increasing the pH of the skin's surface. The decrease in the expression of type I procollagen is a consequence of the decrease in connective tissue growth factor (CTGV) and transforming growth factor (TGF-beta). Finally, transformations in the immune barrier lead to the appearance of conditions and other conditions common to aging skin. (MESA – ARANGO et al., 2017).

Telomere shortening and metabolic oxidative damage then play a crucial role. According to Papanagiotou et al. (2009), no significant differences were found in telomere shortening between sun-exposed and sun-protected sites, probably due to telomerase activity induced in places exposed

to the sun or because stem cells with telomerase activity replace the epidermis. Growing evidence indicates that intrinsic aging and extrinsic aging have converging biochemical and molecular pathways.

Sunlight displays electromagnetic waves across a broad spectrum, including the Ultraviolet (UV-C, UV-B, UV-A), visible, and infrared regions. UVB (wavelength 280-310 nm) is absorbed primarily in the epidermis, while UVA (wavelength 320-400 nm) penetrates deeper by interacting with fibroblasts in the epidermis. UVB directly damages DNA, while UVA causes indirect mutations in DNA through the generation of reactive oxygen and nitrogen species (ROS and ERNs) that photosensitize endogenous molecules (flavin coenzymes, porphyrins, melanins). When photosensitizers produce a greater amount of ROS and ERNs than the cellular capacity to suppress these species, a redox imbalance is characterized, which causes damage to biomolecules such as nucleic acids, lipids and proteins. These lesions can lead to cell death or other phenotypic and genotypic transformations and also stimulate the release of pro-inflammatory cytokines (CHIARELLI-NETO, 2014).

UV irradiation triggers the production of pro-inflammatory cytokines and growth factors. These mediators increase the expression of matrix metalloproteinases (MMPs 1, 3, 8, and 9) through activation of activation protein-1 (AP-1) and/or transcription factor NF-κB, resulting in degraded collagen and elastin in the skin. ROS induced by UV irradiation extinguish the expression of transforming growth factor (TGF) -β, which is a signaling mediator that enables the formation of collagen. Therefore, the increase in the production of EROS after exposure to UV irradiation can degrade the structural integrity of the skin, altering the collagen and elastin components in the dermis, causing skin aging, characterized by deep wrinkles, coarse textures, telangiectasia and pigmentation. The formation of ROS induced by UV irradiation has been suggested as a mutagenic factor in certain skin cancers; for example, squamous cell carcinoma and the p53 gene, leading to precursor lesions to malignancy (PARK, 2015).

The most consistent histological changes of intrinsic skin aging include the flattening of the dermal-epidermal junction. The Result This is a considerably smaller contact surface between the epidermis and dermis, which leads to less communication and transfer of nutrients. Aging skin is relatively acellular and avascular and is characterized by loss of capillary loops and decrease in dermal fibroblasts and extracellular matrix. The functional changes that occur are: slow wound healing due to decreased keratinocyte and fibroblast proliferation capacity, decreased cytokine production, and delayed recovery of barrier function after damage. The decrease in lipid synthesis capacity affects the barrier function, increasing water loss (MESA-ARANGO, 2017).

The lack of response of cutaneous immunity is related to decreased production of immune cytokines and decreased density of Langerhans cells. The decrease in the number of melanocytes

contributes to the reduction of protection against UVA rays, increasing susceptibility to cancer and the risk of cell mutations, which is inversely related to the decrease in the rate of DNA repair. Changes in the architecture of the vessel walls contribute to vascular fragility and impaired thermoregulation. The mechanism of formation of active forms of vitamin D by the skin decreases along with the perception of light touch and vibratory sensation (LANDAU et al., 2007; MESA-ARANGO, 2017).

Extrinsic aging, on the other hand, is related to environmental and lifestyle factors such as smoking, products from burning car fuel, alcohol consumption, eating habits, and industrial waste. Ultraviolet (UV) radiation from the sun or artificial sources has a deleterious effect on skin functions and the survival of keratinocytes, a process known as photoaging. Also, according to recent data, visible light and infrared radiation can also cause damage to the skin (MESA-ARANGO, 2017).

The dermal histopathological changes observed in the photodamage of aged skin are represented by the decrease of collagen and its precursors, in addition to the replacement of elastic fibers by amorphous material. Photodamage causes an inflammatory process, stimulating the proliferation of lymphocytes, mast cells and macrophages, in addition to increasing capillary fragility. Skin chronically exposed to the sun presents thickening of the stratum corneum, with acanthotic epidermis and dysplasia with anaplasia and cellular atypia. Keratinocytes transform into irregular cells with loss of polarity and disordered melanocytes (COSTA et al., 2015).

An experiment was carried out by Baroni et al. (2012) with the aim of To evaluate the influence of aging on the skin quality of white women through the analysis of dermal collagen. Preauricular flaps from 218 Caucasian women who spontaneously underwent facial aesthetic plastic surgery were collected for histological and morphometric analysis. The Picrosirius ultrared staining method was used for quantification and analysis of collagen in five age groups (<40 years, 40 to 49 years, 50 to 59 years, 60 to 69 years, and 70 to 79 years).

Qualitative and degenerative changes were observed in the dermis, with loss of total collagen and its fractions I and III; disorganization and fragmentation of collagen fibers, especially in women over 60 years of age. An agglomeration of amorphous material was observed, resulting from the increase in the density of the elastic material, with modification of the quality and organization of the elastic fibers; The number of blood vessels was not significantly influenced. Shao et al. (2018) produced a study of atomic force microscopy (AFM) and nanoindentation techniques to evaluate the physical properties (surface roughness, stiffness, and hardness) of the extracellular matrix in the photodamaged (forearm) and sun-protected (armpit) human dermis. They concluded that the clinical characteristics of photoaged skin, such as fragility and wrinkles, are the result of changes in dermal collagen fibrils. It has been revealed that the dermal connective tissue of photodamaged skin is characterized by deteriorated and disorganized collagen fibrils, as well as massive accumulation of

aberrant elastic material (solar elastosis), when compared to sun-protected skin. The high number of matrix metalloproteinases (MMPs) are responsible for the mechanical properties found in photoaged skin, as they degrade collagen fibrils in the skin. These altered collagen fibrils impair the normal architecture of the skin's connective tissue and produce a tissue microenvironment that is more prone to skin disorders such as cancer in the elderly and delayed wound healing.

Another consistent characteristic of aged and photoaged skin is the flattening of the epidermal-dermal junction, evidenced in histological sections, such as loss of epidermal ridges and disappearance of papillary projections. The papillae practically disappear and the junction with the atrophic epidermis is a straight line, unlike the dimples seen in younger skin. The depth of interdigitation of the epithelial extensions that protrude into the connective tissue and dermal papillae decreases with age. Corneocytes and cells in the granular layer of aging skin become larger as a result of an epidermal mais lenta (Sauermann et al., 2004).

Regarding collagen, this is the most abundant protein produced by mammals and is fundamental in the constitution of a contiguous interstitium throughout the epidermis. Type I and III collagen occur in greater quantities in human skin than the other types and are maintained in fixed proportion to each other in normal skin tissue. With increasing age, according to a study conducted by Gref et al. (2020) that evaluated the skin of donors between 18 and 50 years of age, it was possible to conclude that the amount of collagen III decreases significantly with age.

Wlaschek et al. (2021) point to growing evidence that skin aging is significantly accelerated by the accumulation of senescent dermal fibroblasts. The fact that natural killer defense cells are unable to properly remove senescent fibroblasts from the tissues contributes to this state. Senescent fibroblasts are responsible for the release of secretory factors and tissue-degrading pro-inflammatory vesicles associated with senescence and skin aging. Collectively, fibroblast depletion during aging with concomitant accumulation of senescent fibroblasts contributes to skin aging.

According to the theory of free radicals, aging can be associated with a greater accumulation of cellular lesions resulting from reactive oxygen and nitrogen species derived from mitochondrial metabolism. As already reported in this work, this oxidative stress leads to an accumulation of oxidized lipids, proteins, carbohydrates and DNA. However, there is also the Theory of Biogenesis based on the maintenance of mitochondrial metabolism and, in this way, oxidative stress is reduced and the aging of the organism as a whole is delayed. The Theory of Biogenesis points to some factors that contribute to this condition, such as: regular physical exercise, caloric restriction, intake of nutritional antioxidants and all this contributes to the increase in the production of cellular antioxidants (SILVA; FERRARI, 2011).

Sander et al. (2002) analyzed biopsies from patients with histologically confirmed solar elastosis. For this, the skin of the buttocks of 12 individuals was exposed to ultraviolet light for 10

days and compared with unexposed contralateral sites. UVA irradiation increased protein oxidation in human fibroblasts in a dose-dependent manner. Similarly, UVB irradiation at sub-cytotoxic doses in human keratinocytes also led to protein oxidation. In addition, hydrogen peroxide (H2O2), one of the main ROS responsible for the deleterious effects of UVA irradiation, and which has been shown to be generated intracellularly in keratinocytes after UVB irradiation, was able to induce the oxidation of proteins in fibroblasts and keratinocytes. This process, however, can also involve other ROS generated by UVA and UVB exposure, such as singlet oxygen. Conclusive evidence is presented for a link between solar elastosis and oxidative protein damage in human skin. In addition, oxidative stress is likely to be involved in the breakdown of the skin barrier after acute UV exposures. These results provide a rationale for the development of efficient antioxidant strategies to prevent photoaging and acute photodamage to the skin.

VITAMIN C

Vitamin C or Ascorbic Acid (AA) was identified in the early twentieth century by British Navy physician James Lind in search of a substance whose deficiency would cause scurvy. In 1747 he documented the ingestion of citrus juices in the treatment of scurvy, carrying out the first known controlled study in medicine. In 1919 Drummond proposed calling the antiscorbutic factor "C". In 1928, the Hungarian scientist Albert von Szent-Gyorgyi discovered and isolated the anti-scurvy factor in several foods, calling it vitamin C. Reichstein and collaborators, in 1933, published the syntheses of D-ascorbic acid and L-ascorbic acid, which still form the basis of the industrial production of vitamin C. They proved that the synthesized L-ascorbic acid has the same biological activity as the natural substance. However, what popularized vitamin C was the research of the American chemist Linus Pauling, winner of the Nobel Prize. Pauling recommended megadoses of the vitamin to combat colds, flu and other viruses, as well as to prevent cancer and other degenerative diseases (MANELA-AZULAY et al., 2003).

Vitamin C is found in two forms in nature: reduced or oxidized (dehydroascorbic acid); The two are equally active, but the oxidized form occurs much less in natural substances. Vitamin C internally in the body fits on both sides of the oxide-reduction reaction. Which adds or removes hydrogen atoms from a molecule. When it undergoes oxidation, it forms dehydroascorbic acid by removing two hydrogen atoms. It is reduced by the addition of two hydrogen atoms, reforming the acid ascórbico (PADAYATTA & LEVINE, 2016).

Because it is a powerful antioxidant, AA attenuates UV-irradiation-mediated damage to the skin by significantly suppressing the production of free radicals triggered by UV light, protecting cells from oxidative stress. It also has an additional role in wound healing by increasing the synthesis of procollagen and collagen, which stimulate the formation of the skin barrier (PARK, 2015).

Free radicals are atoms that have one or more unpaired electrons in their structure, making them reactive. In the activity of cellular respiration, the formation of free radicals occurs naturally, due to oxidation from cellular metabolism. Free radicals are often beneficial, for example in case of inflammation, helping to fight microorganisms. The excess in the production of oxidants or the depletion of antioxidant defenses causes an imbalance of cellular homeostasis, causing irreversible, gradual and irrevocable damage. The solution presented consists of reducing or delaying the formation of these free radicals, slowing down their degradative action in cells. The concept of antioxidant agents, substances that act by inhibiting cellular oxidation, was then created. Antioxidants help reduce the effects of oxidative stress and lack of oxygen by forming complexes that decrease or stabilize free radical-producing reactions before they affect biological targets in cells. Cumulative oxidative lesions may occur when there is a limitation in the availability of antioxidants (HIRATA et al., 2004).

Vitamin C is a six-carbon cyclic ester that is produced from glucose in the liver of most species, but is not synthesized by humans and non-human primates. A mutation of the DNA encoding gulonolactone oxidase resulted in the absence of an enzyme gulonolactone oxidase, which is essential for the synthesis of the immediate precursor of ascorbic acid, 2-keto-l-gulonolactone. Therefore, when humans do not ingest vitamin C in their diets, a state of deficiency occurs with a wide spectrum of clinical manifestations. The clinical expression of vitamin C deficiency, scurvy, is a lethal condition unless treated appropriately. Vitamin C is an electron donor and therefore a reducing agent because it prevents other compounds from being oxidized. Ascorbic acid donates two electrons from a double bond between the second and third carbons of the 6-carbon molecule. The species formed after the loss of an electron is a free radical. Compared to other free radicals, ascorbyl radical is Relatively stable with a half-life of 10 – 5 seconds, unlike most radical species that have a short life, less than 1 millisecond. This property explains why ascorbate is the preferred antioxidant, being considered a good scavenger of free radicals. In simple terms, a reactive free radical is possibly harmful. When interacting with the ascorbate, the radical will be reduced and the ascorbyl radical formed in its place will be less reactive. The ascorbyl radical, with its unpaired electron, is not a long-lived compound, after losing the second electron, the compound formed is the dehydroascorbic acid more stable than the ascorbyl radical (PADAYATTY et al., 2013).

Oral or topical administration of antioxidant vitamins is a widely used solution when free radicals exceed normal levels in our body. Vitamin C stimulates the synthesis of collagen, acting as a cofactor in the hydroxylation reactions of proline and lysine, which are essential amino acids in the formation of collagen fibers. Vitamin C participates in the integrity of connective tissue, cartilage, bone matrix, tendons, and skin, in addition to being involved in the healing process (COSTA et al., 2015).

Normal skin contains high concentrations of vitamin C, with levels comparable to other tissues in the body and well above plasma concentrations, suggesting active accumulation in the circulation. Most of the skin's vitamin C appears to be in intracellular compartments, with concentrations likely to be in the millimolar range. The absorption of vitamin C from plasma and transport through the layers of the skin are mediated by sodium-specific vitamin C transporters (SVCTS) that are present throughout the body and are also responsible for transport to other tissues. Interestingly, epidermal cells express both types of vitamin C transporter, SVCT1 and SVCT2. This is in contrast to most other tissues, which only express SVCT2. The specific location of SVCT1 in the epidermis is of interest due to the lack of vasculature in this tissue and suggests that the combined expression of both transporters 1 and 2 ensures effective intracellular uptake and accumulation of the vitamin, also demonstrating a high dependence of vitamin C in this tissue. Both transporters are hydrophobic membrane proteins that transport sodium, driving the absorption of vitamin C into cells. C. As well as transporter affinity, vitamin C transport is regulated by the availability of SVCT proteins in the plasma membrane. When plasma levels are low, some vitamin C may be released into the epidermal layer by topical application, although the effectiveness of this depends on the formulation of the cream or serum used on the skin. On the other hand, if plasma levels are saturated, it appears that topical application does not increase the vitamin C content in the skin (PULLAR et al., 2017). It is true that vitamin C benefits the physiology of the human skin because it is one of the main promoters of collagen formation, but it does not penetrate well into the barrier of the stratum corneum of the epidermis because it is hydrophilic. It also has the characteristic of being an unstable compound. When exposed to air, moisture, light, heat, metal ions, oxygen, and bases readily break down into biologically inactive compounds such as 2,3-diketo-L-gulonic acid, oxalic acid, L-threonic acid, L-xrylonic acid, or L-lixonic acid. These properties lead the pharmaceutical industry to invest in studies to design lipid derivative products as excipients for antioxidants in topical formulations (GREF et al., 2020 ; LEE et al. 2016).

Topical antioxidants employed in cosmetics must be absorbed through the skin and released to the target tissue in active form. The physiological benefits of vitamin C in its topical application on the skin are diverse, such as an anti-inflammatory effect allowing it to be used in the treatment of inflammatory dermatoses, autoimmune diseases and photosensitizing diseases. Ascorbic acid has the property of stimulating collagen synthesis and, in prolonged topical treatments, activates the synthesis of fibroblasts to reduce wrinkles caused by age, especially in the periorbital region. Vitamin C can also act synergistically with vitamin E by increasing its potency and regenerating it by donating electrons. In this way, vitamin E returns to its active form (antioxidant). Vitamin C plays an important role in the synthesis of the lipid barrier of the stratum corneum (ceramides) and acts by inhibiting the action of ultraviolet rays (AKATHAR; YAZAN, 2008).

Nusgens et al. (2001) conducted a study to evaluate the effect on cells of a vitamin C preparation applied topically on one side of the upper forearm of postmenopausal women versus placebo on the other side. Through biopsy performed on both sides, the mRNA was measured and the result showed that the mRNA of type I and type III collagen increased by vitamin C and three post-translational enzymes, carboxy- and amino-procola proteinases and lysyl oxidase increased in a similar way. Decorin mRNA was also stimulated, but elastin and fibrillin 1 and 2 were not modified by the vitamin. The expression of matrix metalloproteinases 1, 2 and 9 did not change significantly. The stimulant activity of topical vitamin C was more evident in women with the lowest dietary intake of vitamin C and unrelated to the level of actinic damage. The results show that the functional activity of dermal cells is not maximal in postmenopausal women and can be increased with a supply of Vitamin C.

The enzymes prolyl and lysyl hydroxylase are essential for collagen biosynthesis and ascorbic acid acts as a cofactor of these enzymes, contributing to collagen gene expression. An in vitro study examined intracellular AA levels and their stability when exposed to human skin fibroblasts. In this long-term culture, they also determined the effects on type 1 and type 4 collagen and the gene expression of the sodium-dependent vitamin C transporter (SVCT) when the medium containing 100 μM AA was replaced every 24 h for 5 days to avoid ascorbic acid depletion. The conclusion was that intracellular AA levels remained constant; expression of type 1 and type 4 collagen and SVCT2 mRNA was increased, and type 1 procollagen synthesis was increased (Kishimoto et al., 2012).

Shibuya et al. (2014) in a trial with superoxide dismutase 1 (Sod1)-deficient mice demonstrated that combined treatment with collagen peptide and vitamin C attenuates age-related skin atrophy by reducing oxidative damage. Accumulating evidence suggests that collagen peptide (CP) and vitamin C (VC) are transcription factors that regulate type I collagen in vivo. However, the additive effects of PC and VC on age-related skin changes remain unclear. These findings suggest that combined treatment with PC and VC is effective in cases of age-related skin pathology.

Vitamin C benefits the physiology of the human skin because it is one of the main promoters of collagen formation, but it does not penetrate well the barrier of the stratum corneum of the epidermis, as it is hydrophilic. This characteristic makes the pharmaceutical industry invest in studies to conceive lipid derivative products as antioxidant excipients for topical formulations (GREF et al., 2020).

Melanogenesis is triggered by oxygen free radicals and Vitamin C as a potent antioxidant absorbs these radicals and promotes collagen production. In an experiment with 14 patients, 10% sodium ascorbate (ANa) or ascorbic acid was applied to the dark circles of the lower eyelids, the significant change in the erythema index and also a tendency to dermal thickening became clear. The conclusion was that the ANA can improve the dark circles under the eyes on the lower eyelid by

thickening the eyelid dermis and hiding the dark coloration. Vitamin C alone does not easily penetrate the skin, which may be the reason why studies of its use alone are limited (LIPP; WEISS, 2019).

The application of vitamin C in cosmetic products enables levels that would not be possible to achieve with fruit intake or oral supplementation. Formulations containing biological peptide complexes and vitamin C when applied topically to the skin have been shown to be effective in reducing facial wrinkles, i.e., crow's feet wrinkles, forehead wrinkles, and nasolabial folds. Polypeptides or oligopeptides are made up of amino acids and are able to mimic the sequence of peptides in molecules such as collagen or elastin, acting as messenger molecules in the body. Peptide complexes stimulate fibroblast proliferation, increasing the expression of messenger RNA and procollagen VII and fibril-1. While peptides and vitamin C are established anti-aging ingredients, the formulation is key to keeping antioxidants active and stable. Vitamin C formulated at low pH and the hydrolyzed biological peptide complex of di and tri peptide have been shown to improve bioavailability, improving assimilation by skin cells and passage through the skin barrier (ESCOBAR et al., 2020).

The maximum concentration of topical L-ascorbic acid for percutaneous absorption is 20%. As already mentioned, vitamin C has many anti-aging effects on the skin, not only as a potent antioxidant and mediator of photodamage and melanogenesis, but also through its role in supporting collagen biosynthesis and stability, which provide renewing and anti-inflammatory effects. In addition, vitamin C acts simultaneously with vitamin E, which is also not produced endogenously and must be obtained through the diet. The fat-soluble properties of Vitamin E, which supports cutaneous levels of tocopherols, allow it to pass into the deeper layers of the stratum corneum through secretions from the sebaceous glands, residing within cell membranes and protecting them from oxidative stress. In addition, vitamin E can reduce hyperpigmentation induced by ultraviolet light. Vitamins C and E work synergistically in quenching free radicals. Vitamin C regenerates the oxidized form of vitamin E to its reduced form. Topical use of 15% L-ascorbic acid combined with 1% alpha-tocopherol has been shown to provide significantly greater protection against sunburn cell formation compared to L-ascorbic acid or 19% alpha-tocopherol alone (RATTANAWIWATTPONG et al., 2020).

Vitamin C plays an essential role in connective tissue healing, being a cofactor for prolyl hydroxylase and lysyl hydroxylase. These enzymes catalyze the hydroxylation of proline and lysine residues from procollagen, promoting proper folding of the stable collagen triple helix conformation. In addition to its role in collagen synthesis, vitamin C acts as a powerful antioxidant by neutralizing ROS, deleterious species responsible for cell apoptosis during the inflammatory phase. Cell culture studies have also reported that vitamin C can induce tendon-derived stem cell mobilization,

osteoblast growth and differentiation, and fibroblast stimulation. Therefore, vitamin C has been increasingly studied for its contributions to the treatment of musculoskeletal injuries in clinical trials and in vitro. Although laboratory studies have reported that vitamin C is essential for collagen fiber formation and cell differentiation, there are controversies surrounding the efficacy of vitamin C as a supplement for clinical treatment (DE PHELLIPO et al., 2018).

According to Pinnel et al. (2001), topical use of L-ascorbic acid provides a safe and effective supplement to normal tissue reserves to increase photoprotection, improve wound healing, and increase antioxidant defenses. It must be formulated in high concentration and with a pH of less than 3.5 to be effective. The L-ascorbic acid after being applied to the skin is stabilized and remains in the tissue for a period of days. Magnesium ascorbyl phosphate and ascorbyl-6-palmitate have not been shown to be effective substitutes for L-ascorbic acid in topical formulations, despite being effective for oral use.

MICRONEEDLING

Microneedling, also known as Percutaneous Collagen Induction Therapy (PCT), is a non-invasive method that stimulates the body's own regenerative mechanisms and has been gaining a lot of space in a specific niche of patients who want treatments with little or no recovery and that offer good results. Although laser therapy is a long time ago, Long considered the treatment of choice for photoaged skin, microneedling has recently been indicated for a wide range of applications, including skin rejuvenation, acne scars, treatment of rhytids, surgical scars, dyschromia, melasma, enlarged pores, and as a carrier of rejuvenating actives. According to the American Society for Plastic Surgery, minimally invasive non-surgical procedures accounted for approximately 89% of all cosmetic procedures performed in 2015 (ALSTER; GRAHAM, 2017).

In 1995, Orentreich and Orentreich described the term "subcision" to release fibrous strands responsible for depressed scars and retracted wrinkles of the skin, as being a means of stimulating the connective tissue underneath them. Desmond Fernandes, in the same period and independently, used a similar technique to treat the upper lip by inserting a 15G needle into the skin producing tunnels parallel to the surface, under the wrinkles, in various directions. Camirand and Doucettreated used a tattoo gun to treat scars by stimulating an abrasion with a needle. This tattooing technique was too superficial to obtain good effects on deeper scars or to activate colonogenesis in the reticular dermis. The needles need to penetrate deeper to stimulate the production of elastic fibers from the inner layers of the dermis towards the surface. All of these techniques are based on the principle that the needles break down the old collagen fibers in the most superficial layer of the dermis that limits scars or wrinkles. This process causes the removal of damaged collagen and induces the production of more collagen just below the epidermis. Based on this knowledge, Desmond Fernandes designed a

special device for microneedling consisting of a rolling cylinder with microneedles at regular intervals (FABROCCINI et al., 2009).

Ablative modalities such as lasers, peels, and dermabrasion are based on partial removal of the epidermis to trigger the growth of new skin to replace scar tissue or aging tissue. However, damaging the deeper layers of the skin carries the risk of prolonged healing periods, fibrosis of the papillary dermis, excessive scarring, increased photosensitivity, and irregular pigmentation. These problems have led to the development of non-ablative methods that owe their efficacy to the stimulation of dermal neocollagenesis, preserving the stratum corneum and epidermal barrier function. The use of energy (e.g., non-ablative lasers, fractional lasers, and intense pulsed light) for this purpose still causes some thermal injury and necrosis, while the use of small needles for percutaneous collagen induction reaches the papillary and reticular dermis through channel formation in a purely mechanical process. Each individual microlesion is perceived by the skin as a lesion, but as the epidermal barrier is minimally disrupted, it triggers the entire healing process without scarring (RAMAUT et al., 2017).

The basic principle of microneedling is the repetitive use of the device on the skin in various directions (horizontal, vertical, and oblique) applying some pressure to achieve an even distribution of the holes; The procedure is then repeated as needed at varying intervals. Microneedling can be administered through various types of devices, which can be divided into: manual, motorized and radio frequency coupled. Hand-held devices include rotating drums as well as static devices; The latter allow the treatment of smaller and more localized scars (LOSIFIDIS; GOUTOS, 2019). The needles of the devices range from 0.25mm to 3.0mm in length.

In motorized (pen-type) devices, the depth of penetration of the needles can be adjusted based on the site to be treated. The speed also varies from 10,250rpm to 27,750 rpm, depending on the type of device. Sterile disposable needle cartridges feature varying amounts of needles (12/32 gauge and 36/30 gauge) that are used to customize therapy based on the specific treatment site. Typically, where the skin is thinner, such as the skin of the forehead, lower eyelids, and nasal bridge, the needles used for treatment range from 0.5 to 1.0 mm, while the cheeks, perioral regions, and scars or stretch marks on various parts of the body are typically treated with needle depths of 1.5 to 3.0 millimeters. As a general rule, for more fibrotic skin, treatment with longer needles can be used (LOSIFIDIS; GOUTOS, 2019).

The microneedling procedure is performed under topical anesthesia by rolling the device over the skin back and forth, with the same pressure, in various directions, so that the holes have an even distribution. The epidermis is only pierced and recovers quickly as the microneedles penetrate the epidermis but do not remove it. The action of the needles separates the cells from each other without cutting them, ridding many cells. Because they are arranged in a cylinder, the needles initially

penetrate the skin at an angle, deepening as they that the cylinder rolls. The needle enters and exits the skin for approximately 1.5 to 2 mm, in a circular motion associated with the bearing. The epidermis, and especially the stratum corneum, remain "intact" except for the tiny holes made by the needles—each about four cells in diameter. When penetrating, the needle causes a localized injury and minimal bleeding due to the rupture of the blood vessels. Wound healing develops in three phases: inflammation, proliferation, and remodeling; and culminates in the formation of new collagen in the upper dermis just below the basal layer of the epidermis (FABROCINI et al., 2009; FERNANDES; SIGINIORI, 2007).

Fernandes (2005) explains very clearly the mechanism of action of Percutaneous Collagen Induction. When the needles penetrate the skin, they cause thousands or tens of thousands of fine, which are next to each other and a field effect is obtained and the bleeding is practically confluent. Then the three phases of wound healing are fulfilled: Phase I: Inflammation, which begins immediately after the injury Phase II: Proliferation (tissue formation), which begins after about 5 days and lasts about 8 weeks Phase III: Tissue remodeling, 8 weeks to 1 year. Fibroblasts are primarily responsible for tissue remodeling. On the fifth day after injury, the fibronectin matrix is deposited along the axis on which the fibroblasts are aligned and on which collagen will be deposited. TGFb-3 and other growth factors play an important role in the formation of this matrix. Type III collagen is deposited in the upper dermis just below the basal layer of the epidermis. Type III collagen is gradually replaced by type I collagen over a period of a year or more, which increases tensile strength. Matrix metalloproteinases (MMPs) are essential for the conversion process. The various MMPs are generally classified as MMP-1 (collagenases), MMP-2 (gelatinases), and MMP-3 (stromellisins).

Although microneedling is a minimally invasive treatment, Alster and Graham (2017) warn about the contraindications and precautions to be taken in clinical practice. Contraindications include inflammatory acne, active cold sores or other local infection in the treatment area, predisposition to keloid, and immunosuppression. In addition, caution should be exercised with concomitant microneedling near botulinum toxin injection sites to avoid potential unintentional diffusion of the toxin. Although any skin phototype can be treated, it is recommended that treatment be delayed in patients with a history of of recent sun exposure (or who are visibly tanned) until all traces of tanning disappear to prevent post-treatment depigmentation. In darker skin phototypes (Fitzpatrick IV, V, VI), there was a concern about depigmentation, but clinical experience shows that this undesirable effect is rarely seen in areas of microneedling treatment. A histological analysis of skin melanocytes 24 hours after microneedling showed no change in the number of melanocytes nor any epidermal rupture. One week of oral antiviral therapy is recommended in patients with a history of cold sores as a prophylactic measure (starting on the day of treatment) to minimise the risk of reactivation of the

virus. The most common and expected side effects of treatment include mild erythema, localized swelling, and peeling of the skin, which typically resolves within 48 to 72 hours. Spot bleeding is self-limiting and disappears within minutes of the procedure with gentle hand pressure and gauze soaked in ice water. The use of topical medications with or immediately after the microneedling procedure may increase the incidence of adverse effects due to the creation of channels within the epidermis and dermis that act as a gateway to the body, allowing the development of an immune response to immunogenic particles. Therefore, it is imperative to advise patients to avoid over-the-counter skin care products in the first week after the microneedling procedure, as they may induce a local or systemic hypersensitivity reaction.

The efficacy and tolerance of microneedling treatment on facial skin significantly improve wrinkles, fine lines, sagging and skin texture, in an assessment made between 90 and 150 days after the first treatment. This result was presented by Ablon (2018) in an experiment with 48 individuals aged between 35 and 75 years old. The treatment protocol used was four sessions with 30-day intervals. Side effects were minimal and easily controlled when compared to more invasive therapies such as laser and radiofrequency. The treatment was well tolerated with minimal pain, discomfort and recovery time.

A study was carried out at Al-Minya University in Egypt by El-Domyati et al. (2015) with the aim of analyzing the efficacy, combined with quantitative evaluation, of histological changes after multiple sessions of microneedling in the treatment of skin aging. The patients had Fitzpatrick wrinkles type III and IV and Glogau wrinkles class II to III, ranging in age from 38 to 60 years. They were underwent six sessions of cutaneous microneedling at 2-week intervals. Standard photographs and skin biopsy samples were obtained at one month and three months after the start of treatment. The result showed that cutaneous microneedling produced a remarkable clinical improvement of the photoaged skin, also confirmed at the histological level. Compared to baseline, collagen types I, III, and VII, as well as newly synthesized collagen along with tropoelastin, showed a statistically significant increase ($p<0.05$) in response to treatment, while the mean total elastin level decreased significantly ($p<0.05$) after treatment. Cutaneous microneedling has been observed to be a promising option for minimally invasive treatment with the advantage of increasing collagen production. However, it usually takes several sessions to maintain the improvement achieved.

Microneedling is a safe and effective treatment for both wrinkles caused by natural aging and wrinkles caused by smoking. This was the conclusion of a study conducted by Armed et al. (2018) where forty patients were examined: twenty men, all smokers (of whom only eight agreed to participate in the study) and twenty women with facial wrinkles and non-smokers (all agreed to participate in the study). The selected patients underwent six sessions of dermapen, with a two-week interval between sessions. All showed improvement in the signs of aging without side effects, except

for edema and redness, which disappeared within 2 to 3 days.

In a pilot study, Travers et al. (2019) tested the ability of microneedling therapy to regulate IGF-1 dermal levels and normalize the acute pro-carcinogenic UVB response, thereby reducing the incidence of non-melanoma skin cancer associated with aging, as geriatric skin responds to pro-carcinogenic UVB radiation in a manner that allows tumor cells to develop. Geriatric volunteers were treated with a microneedling device on the skin of the buttocks and 3 months later IGF-1 levels and UVB responses were tested on the injured skin and control skin. Microneedling wounds resulted in a decrease in the number of senescent fibroblasts, an increase in dermal levels of type I collagen and IGF-I, and increased protection against keratinocytes with DNA damage caused by UVB radiation.

According to Devgan et al. (2019), patients who underwent microneedling therapy reported 80% to 85% overall satisfaction with the results obtained and argue that it is the procedure of choice for individuals who They want to treat their skin with minimal exposure to chemicals, feeling little pain, and with a short recovery time.

MICRONEEDLING ASSOCIATED WITH THE USE OF VITAMIN C

The skin is a multi-layered physicochemical barrier that protects the human body. The stratum corneum is the outermost keratinized layer of the skin through which only molecules less than or equal to 500 Da (Dalton) can move freely through it. This property, added to the low permeability of Vitamin C, is a factor that limits its delivery within the skin tissue, restricting a variety of biological, pharmaceutical and dermatological functions. Therefore, several non-invasive technologies, including microneedling, in addition to intensifying chemical penetration, have been developed to circumvent or modulate the skin barrier by physical means. This process that combines microneedling with the topical application of an active ingredient on the surface of the skin is called *drug delivery* (LEE et al., 2016).

Palheta et al. (2018) evaluated in one study the effect of using andiroba oil compared to Vitamin C as *drug delivery* in the microneedling procedure on rat skin. They used 31 male rats divided into five groups: GPi (pilot), with three animals; GM (microneedling); GMA (microneedling + andiroba); GMV (microneedling + vitamin C); and GOM (microneedling + mineral oil), with seven animals in each group. The animals were submitted to the microneedling technique on D0 (day 0) and to the application of the substance of their respective group on the skin in the morning for seven days. The result obtained showed that the group that received andiroba oil obtained lower results when compared to vitamin C. In the animals in which vitamin C was used, greater dermal thickness, greater proliferation of collagen fibers and fibroblasts and better angiogenesis were observed.

Acne scars occur mostly on the face and impact people's self-esteem, which explains the great demand for professionals who treat these marks. Microneedling, due to its collagen-inducing

property, has been widely used as a therapy for acne scars. Chawla, S. (2014) conducted a study where they clinically evaluated the results, from one side of the face of Platelet-Rich Plasma (PRP) Microneedling and 15% Vitamin C Microneedling. The conclusion was that microneedling associated with PRP has superior results to microneedling with Vitamin C.

The combination of mesotherapy with microneedles and Vitamin C-based products has been used to treat mature skin that has dehydration, hyperpigmentation and loss of elasticity. Microneedling enhances the absorption of the substance into the skin and this therapy has shown improvement in the degree of firmness, hydration and skin tone. This was the conclusion reached by Markiewicz et al. (2018) when they analyzed the results of the application of a 20% L-ascorbic acid solution (ph 3.5) prepared immediately before use. For this purpose, seventeen volunteers, aged between 45 and 70 years, collaborated, where 4 applications of the therapy were performed, one every 10 days, using devices with microneedles of 0.5 mm in length.

In another study (MENON et al., 2020) they verified the action of vitamin C on melasma, which is a pigmentary disorder that affects the face and is not easy to treat. Its pathogenesis is not defined, although some risk factors have already been identified. This study made a comparison of microneedling with Vitamin C, but this time the comparison was with tranexamic acid (TXA). The study lasted 8 weeks where the faces of 30 female patients with melasma were divided for aviation of the two types of treatment. The result showed that both tranexamic acid and vitamin C are effective for the treatment of melasma. However, TXA has been shown to be more effective, although this improvement is not statistically significant.

Tahoun et al. (2021) also studied the efficiency of tranexamic acid *versus* vitamin C, both of which are associated with microneedling therapy. In conclusion, both therapeutic modalities have been shown to be successful and well-tolerated for the treatment of melasma with minimal side effects. Tranexamic acid surpasses the result of vitamin C in relation to the vascular component of melasma, because through dermoscopy it is possible to visualize the disappearance of telangiectatic blood vessels. Vitamin C, however, leads where pigmentation is the main factor. The suggestion is to perform sequential treatments of TXA and vitamin C with microneedling to increase the therapeutic effect.

DISCUSSING THE DATA

The aging process is inevitable. All cells in the body undergo modifications that affect the entire physiology of the tissues, and the skin is no different. Several authors (CHIARELLI-NETO, 2014; LADAU et al., 2007; MESA ARANGO et al., 2017; PARK, 2015; SILVA and FERRARI, 2011) relate the skin aging process to the action of ROS.

Normally, ROS have an essential function for the body as they enable several biochemical

reactions for the physiology of tissues, among these reactions the formation of ATP, an important molecule that generates energy for the cell (COSTA et al., 2015). However, with the aging process, ROS begin to present undesirable effects, causing impairments to cellular metabolism such as mutations, decreased protein function, decreased cell transport and transmembrane signaling (LADAU et al., 2007).

The skin aging process occurs through intrinsic factors – associated with the individual's genetic characteristics and extrinsic factors – associated with the environmental conditions in which we live and lifestyle (BARONI et al., 2012; MESA-ARANGO, 2017). However, according to the reports of several authors (CHIARELLI NETO, 2014; MESA-ARANGO, 2017; PARK, 2015; SANDER et al., 2002), talvez a

Solar radiation is the main representative of extrinsic factors for skin aging. So much so that, many times, when referring to aging, they use "photoaging" as an integral term to the process.

In this way, in addition to the senescent physiological process being able to generate EROS, solar radiation is also capable. The impairments that can be observed in this process include changes in dermal collagen fibrils, flattening of the epidermal-dermal junction, disordered melanocytes, accumulation of senescent fibroblasts, increased volume of corneocytes and cells of the granulosa layer of the skin due to slower cell renewal (COSTA et al., 2015; GREF et al., 2020; SAUERMANN et al., 2004; SHAO et al., 2018; WLASCHEK et al., 2021). Clinically, aged, or photoaged, skin presents, among other findings, fragility and wrinkles (SHAO et al.; 2018).

If, at a given moment, ROS exceeds our body's ability to defend itself, antioxidant substances can be used to promote its neutralization. One of these substances is vitamin C. In addition to its anti-inflammatory and antioxidant action, vitamin C, as a cofactor for collagen synthesis, stimulates the synthesis of this substance by fibroblasts and can be used systemically or topically (COSTA et al., 2015). During the aging process, the stimulation of collagen production is extremely important to return the skin to its desirable clinical characteristics, as it is the main component of the dermis, about 70% to 80% of its composition, is type I and III collagen, which confers resistance to the tissue (BARCAUI et al., 2014; CESTARI, 2018).

Although normal skin contains high concentrations of vitamin C (PULLAR et al., 2017), humans are not able to synthesize it and must obtain it from the diet, otherwise they can develop severe clinical manifestations that can even be lethal (PADAYATTY et al., 2013). Thus, in addition to the use of vitamin C as a therapy for skin aging, its importance for the physiology of the whole body should not be forgotten and is necessary for the general health of the patient.

Some authors (GREF et al., 2020; LIPP and WEISS, 2019; PULLAR et al., 2017) point out the difficulty of vitamin C crossing the epidermal barrier when used topically, but ESCOBAR et al (2020) argue that the application of vitamin C in cosmetic products enables levels that would not be

possible to achieve through diet or oral supplementation and that, when formulated at low pH and as a hydrolyzed biological peptide complex of di and tripeptide, it has greater bioavailability, assimilation by keratinocytes and passage through the cutaneous barrier.

The anti-aging effect of Vitamin C on the skin is well recognized, not only as a potent antioxidant and mediator of photodamage and melanogenesis, but also as an inducer of collagen biosynthesis and stability, which provide renewing and anti-inflammatory effects (AKATHAR and YAZAN, 2008; DEPHILLIPO et al., 2018; ESCOBAR et al., 2020; PARK, 2015; RATTANAWIWATTPONG et al., 2020). Thus, the use of vitamin C could be an intelligent strategy when associated with another technique that proposes the treatment of skin aging, such as microneedling.

As already mentioned, vitamin C has a limiting characteristic, which is its low skin permeability (GREF et al., 2020; LIPP and WEISS, 2019; PULLAR et al., 2017). Thus, microneedling, which is a technique that, in addition to stimulating the body's own regenerative mechanisms, including rejuvenation (ALSTER and GRAHAM, 2015), promotes the formation of tiny channels in the skin (FABROCINI et al., 2009; FERNANDES and SIGINIORI, 2007) that can take VC to depths that it would not reach alone when applied topically (LEE et al., 2016).

Several authors (MARKIEWICZ et al., 2018; MENON et al., 2020; MUSTAFA et al., 2021; PALHETA et al., 2018) reported the synergistic effect of the association between VT and microneedling. The *drug delivery* of VC provided by microneedling, which is a non-invasive technique with little risk of causing serious complications, is capable of promoting effective effects in the treatment of skin aging, reducing sagging and superficial wrinkles and improving skin texture.

Studies (MENON et al., 2020; MUSTAFA et al., 2021) also indicate the use of VC associated with microneedling for the treatment of melasma. As extrinsic cutaneous aging by UV irradiation, which triggers an increase in the expression of matrix metalloproteinases (MMPs 1, 3, 8 and 9) and extinguishes the expression of transforming growth factor (TGF–β), aging presents, among other clinical findings, skin pigmentation (PARK, 2015) that can also be attenuated through *VC drug delivery* .

The data in the literature suggest that there is a need for further studies to investigate the action of vitamin C and microneedling on pigmentation acquired by the skin aging process, since, as already mentioned, its action on melasma has already been researched, including associating VC with tranexamic acid in sequential applications to increase therapeutic efficacy (MENON et al., 2020; MUSTAFA et al., 2021).

Unequivocally, it is clear that vitamin C associated with microneedling is a therapy indicated for the treatment of aging skin that presents dehydration, hyperpigmentation, and loss of elasticity (MARKIEWICZ et al., 2028).

And, following the same line of reasoning, it would be interesting to implement *home care* containing VC for the continuity of outpatient treatment because it has the property of stimulating collagen synthesis in prolonged topical treatments, activating fibroblasts (AKATHAR and YAZAN, 2008). Despite the limitation of VC in crossing the skin barrier, the pharmaceutical industry has been developing products with lipid derivatives as antioxidant excipients for topical formulations containing VC (GREF et al., 2020).

FINAL THOUGHTS

Microneedling is a safe and effective treatment to treat wrinkles, fine lines, sagging, and improve skin texture, promoting clinical improvement of aging skin.

Vitamin C has several effects on skin aging. In addition to being a powerful antioxidant capable of attenuating the damage caused by UV irradiation, it performs the function of participating in the biosynthesis and stability of collagen that provide rejuvenating effects.

The association of vitamin C during Microneedling Therapy is a synergistic therapy, where the effectiveness of each element is added to promote enhanced results in aging skin that presents dehydration, hyperpigmentation, and loss of elasticity.

REFERENCES

1. Ablon, G. (2018). Safety and Effectiveness of an Automated Microneedling Device in Improving the Signs of Aging Skin. J Clin Aesthet Dermatol., 11(8), 29–34.

2. Akhtar, N., & Yazar, Y. (2008). Formulation and in-vivo evaluation of a cosmetic multiple emulsion containing vitamin C and wheat protein. Pak. J. Pharm. Sci., 21(1), 45–50.

3. Alster, T. S., & Graham, P. M. (2018). Microneedling. Dermatologic Surgery, 44(3), 397–404.

4. Amer, M., Farag, F., Amer, A., et al. (2018). Dermapen in the treatment of wrinkles in cigarette smokers and skin aging effectively. Journal of Cosmetic Dermatology, 17(6), 1200–1204.

5. Azulay, R. D. (2017). Dermatologia (7th ed.). Rio de Janeiro: Editora Guanabara Koogan.

6. Barcaui, E. de O., Carvalho, A. C. P., Piñeiro Maceira, J., et al. (2015). Study of the skin anatomy with high-frequency (22 MHz) ultrasonography and histological correlation. Radiologia Brasileira, 48(5), 324–329.

7. Baroni, E. do R. V., Biondo-Simões, M. de L. P., Auersvald, A., et al. (2012). Influence of aging on the quality of the skin of white women: the role of collagen. Acta Cirurgica Brasileira, 27(10), 736–740.

8. Bohjanen, K. (n.d.). Estrutura e funções da Pele. Retrieved from https://www.booki.pt/userfiles/files/loja/preview/9788580553796.pdf.

9. Cestari, S. (2018). Dermatologia pediátrica (Vol. 2, pp. 9-12). Atheneu.

10. Chawla, S. (2014). Split face comparative study of microneedling with PRP versus microneedling with vitamin C in treating atrophic post acne scars. Journal of Cutaneous and Aesthetic Surgery, 7(4), 209.

11. Chiarelli-Neto, O., Ferreira, A. S., Martins, W. K., et al. (2014). Melanin Photosensitization and the Effect of Visible Light on Epithelial Cells. PLoS ONE, 9(11).

12. Costa de Oliveira, A., Pinto, C., & Baby, A. (2018). Effects of ascorbic acid against skin aging. BWS Journal, 1, 1–7.

13. Costa, A., Pegas Pereira, E. S., Assumpção, E. C., et al. (2015). Assessment of clinical effects and safety of an oral supplement based on marine protein, vitamin C, grape seed extract, zinc, and tomato extract in the improvement of visible signs of skin aging in men. Clinical, Cosmetic and Investigational Dermatology, 8, 319–328.

14. DePhillipo, N. N., Aman, Z. S., Kennedy, M. I., et al. (2018). Efficacy of Vitamin C Supplementation on Collagen Synthesis and Oxidative Stress After Musculoskeletal Injuries: A Systematic Review. Orthopaedic Journal of Sports Medicine, 6(10).

15. Devgan, L., Singh, P., & Durairaj, K. (2019). Minimally Invasive Facial Cosmetic Procedures. Otolaryngologic Clinics of North America, 52(3), 443–459.

16. El-Domyati, M., Barakat, M., & Awad, S. (2015). Multiple microneedling sessions for minimally invasive facial rejuvenation: an objective assessment. International Journal of Dermatology, 54(10.111/ijd.12761), 1361–1369.

17. Ellinger, S., & Stehle, P. (2009). Efficacy of vitamin supplementation in situations with wound healing disorders: results from clinical intervention studies. Current Opinion in Clinical Nutrition and Metabolic Care, 12(6), 588–595.

18. Escobar, S., Valois, A., Nielsen, M., et al. (2020). Effectiveness of a formulation containing peptides and vitamin C in treating signs of facial ageing: three clinical studies. International Journal of Cosmetic Science, 43(2), 131–135.

19. Evans, J. R., & Lawrenson, J. G. (2017). Antioxidant vitamin and mineral supplements for preventing age-related macular degeneration. Cochrane Database of Systematic Reviews, (7), CD000253.

20. Farris, P. K. (2006). Topical Vitamin C: A Useful Agent for Treating Photoaging and Other Dermatologic Conditions. Dermatologic Surgery, 31, 814–818.

21. Fernandes, D. (2005). Minimally Invasive Percutaneous Collagen Induction. Oral and Maxillofacial Surgery Clinics of North America, 17(1), 51–63.

22. Fernandes, D., & Signorini, M. (2008). Combating photoaging with percutaneous collagen induction. Clinics in Dermatology, 26(2), 192–199.

23. Ferreira, A. S., Gandra, M. F., Freitas, C. de A., et al. (2020). Suplementação de colágeno e outras formas de tratamento no combate ao envelhecimento cutâneo. Revista Eletrônica Acervo Científico, 12, e4653.

24. Garbin, A., & Wakayama, S. (2019). Orofacial harmonization and its implications in dentistry. Brazilian Journal of Surgery and Clinical Research, 27(2), 116–122.

25. Gref, R., Deloménie, C., Maksimenko, A., et al. (2020). Vitamin C–squalene bioconjugate promotes epidermal thickening and collagen production in human skin. Scientific Reports, 10(1).

26. Hirata, L., Sato, M. E., & Costa, C. A. (2004). Radicais Livres e o Envelhecimento Cutâneo. Acta Farm. Bonaire's, 23(3), 418–24.

27. Ismail, E. S. A., Patsatsi, A., Abd El-Maged, W. M., et al. (2019). Efficacy of microneedling with topical vitamin C in the treatment of melasma. Journal of Cosmetic Dermatology, 18(5), 1342–1347.

28. Junqueira, L. C. U. (2018). Histologia Básica: texto e atlas (13th ed.). Rio de Janeiro: Guanabara Koogan.

29. Kishimoto, Y., Saito, N., Kurita, K., et al. (2013). Ascorbic acid enhances the expression of type 1 and type 4 collagen and SVCT2 in cultured human skin fibroblasts. Biochemical and Biophysical Research Communications, 430(2), 579–584.

30. Kwon, S.-H., Choi, J.-Y., Ahn, G. Y., et al. (2019). The efficacy and safety of microneedle monopolar radiofrequency for the treatment of periorbital wrinkles. Journal of Dermatological Treatment, 32(4), 460–464.

31. Landau, M. (2007). Exogenous factors in skin aging. Current Problems in Dermatology, 35, 1–13.

32. Lee, Y. I., Kim, E., Lee, D. W., et al. (2021). Synergistic Effect of 300 μm Needle-Depth Fractional

Microneedling Radiofrequency on the Treatment of Senescence-Induced Aging Hyperpigmentation of the Skin. International Journal of Molecular Sciences, 22(14), 7480.

33. Lins, V. F., Brandão, D. G., & Rocha, S. M. W. (2021). A utilização da fibrina rica em plaquetas em procedimentos estéticos orofaciais: uma revisão integrativa. Research, Society and Development, 10(3), e27910313477.

34. Lipp, M., & Weiss, E. (2019). Nonsurgical Treatments for Infraorbital Rejuvenation. Dermatologic Surgery, 45(5), 700–710.

35. Mandl, J., Szarka, A., & Bánhegyi, G. (2009). Vitamin C: update on physiology and pharmacology. British Journal of Pharmacology, 157(7), 1097–1110.

36. Manela-Azulay, M., Mandarim-de-Lacerda, C. A., Perez, M. A., et al. (2003). Vitamina C. Anais Brasileiros de Dermatologia, 78, 265–272.

37. Markiewicz, A., Zasada, M., Erkiert-Polguj, A., et al. (2018). An evaluation of the antiaging properties of strawberry hydrolysate treatment enriched with L-ascorbic acid applied with microneedle mesotherapy. Journal of Cosmetic Dermatology, 18(1), 129–135.

38. Mesa-Arango, A. C., Flórez-Muñoz, S. V., & Sanclemente, G. (2017). Mechanisms of skin aging. Iatreia, 30(2), 160-170. DOI 10.17533/udea.iatreia.v30n2a05.

39. Novais, M. de J. A., & Souza, É. P. de. (2020). Utilização de Tratamentos Estéticos no Retardo do Envelhecimento Cutâneo: Revisão Integrativa / Use of Aesthetic Treatments to Delay Cutaneous Aging: Integrative Review. ID on line REVISTA DE PSICOLOGIA, 14(53), 950–961.

40. Nusgens, B. V., Colige, A. C., Lambert, C. A., et al. (2001). Topically Applied Vitamin C Enhances the mRNA Level of Collagens I and III, Their Processing Enzymes and Tissue Inhibitor of Matrix Metalloproteinase 1 in the Human Dermis. Journal of Investigative Dermatology, 116(6), 853–859.

41. Padayatty, S. J., & Levine, M. (2016). Vitamin C: the known and the unknown and Goldilocks. Oral Diseases, 22(6), 463–493.

42. Palheta, C. da S. A., Silva, P. R. G. da, Oliveira, A. C. M. de, et al. (2018). Efeitos da andiroba associada ao microagulhamento na pele de ratos. Surgical & Cosmetic Dermatology, 10(4).

43. Papanagiotou, V. D. (2009). Skin aging and Photoaging. 2nd Department of dermatology and Venereology University of Athens. Greece., 4, 57–65.

44. Park, K. (2015). Role of Micronutrients in Skin Health and Function. Biomolecules & Therapeutics, 23(3), 207–217.

45. Pereira, A. C., Martins, F. S., & Barbosa, L. (2021). Indução percutânea de colágeno associada ao ácido ascórbico no tratamento de rejuvenescimento facial. Research, Society and Development, 10(8), e58310817645.

46. Pinnell, S., Yang, H., & Omar, M. (2001). Topical L-Ascorbic acid: percutaneous absorption studies. Dermatol Surg, 27, 137–142.

47. Pullar, J. M., Carr, A. C., & Vissers, M. C. M. (2017). The Roles of Vitamin C in Skin Health. Nutrients, 9(8), 866.

48. Ramaut, L., Hoeksema, H., Pirayesh, A., et al. (2018). Microneedling: Where do we stand now? A systematic review of the literature. Journal of Plastic, Reconstructive & Aesthetic Surgery, 71(1), 1–14. Disponível em: <https://www.sciencedirect.com/science/article/abs/pii/S1748681517302504>.

49. Rattanawiwatpong, P., Wanitphakdeedecha, R. B., Mrungpert, A., et al. (2020). Anti-aging and brightening effects of a topical treatment containing vitamin C, vitamin E, and raspberry leaf cell culture extract: A split-face, randomized controlled trial. Journal of Cosmetic Dermatology, 19(3), 671–676.

50. Raza, M. H., Iftikhar, N., Anwar, A., et al. (2022). Split-face comparative analysis of micro-needling with tranexamic acid vs vitamin C serum in melasma. Journal of Ayub Medical College Abbottabad, 34(1), 169–172.

51. Sander, C. S., Chang, H., Salzmann, S., et al. (2002). Photoaging is Associated with Protein Oxidation in Human Skin In Vivo. Journal of Investigative Dermatology, 118(4), 618–625.

52. Sanz, A., & Stefanatos, R. K. A. (2008). The Mitochondrial Free Radical Theory of Aging: A Critical View. Current Aging Science, 1(1), 10–21.

53. Sauermann, K., Jaspers, S., Koop, U., et al. (2004). Topically applied vitamin C increases the density of dermal papillae in aged human skin. BMC Dermatology, 4(1).

54. Schmitt, L., Marquardt, Y., Amann, P., et al. (2018). Comprehensive molecular characterization of microneedling therapy in a human three-dimensional skin model. PLOS ONE, 13(9), e0204318.

55. Shao, Y., Qin, Z., Alexander Wilks, J., et al. (2018). Physical properties of the photodamaged human skin dermis: Rougher collagen surface and stiffer/harder mechanical properties. Experimental Dermatology, 28(8), 914–921.

56. Shibuya, S., Ozawa, Y., Toda, T., et al. (2014). Collagen peptide and vitamin C additively attenuate age-related skin atrophy in Sod1-deficient mice. Bioscience, Biotechnology, and Biochemistry, 78(7), 1212–1220.

57. Silva, W., & Ferrari, C. (2011). Metabolismo Mitocondrial, Radicais Livres e Envelhecimento. Rev. Bras. Geriatr.Gerontol., 14(3), 41–45.

58. Tahoun, A. I., Mostafa, W. Z., & Amer, M. A. (2021). Dermoscopic evaluation of tranexamic acid versus Vitamin C, with microneedling in the treatment of melasma: a comparative, split-face, single-blinded study. Journal of Dermatological Treatment, 1–7.

59. Travers, J. B., Kemp, M. G., Weir, N. M., et al. (2019). Wounding with a microneedling device corrects the inappropriate ultraviolet B radiation response in geriatric skin. Archives of Dermatological Research, 312(1), 1–4.

60. Üstüner, P., Balevi, A., & Ozdemir, M. (2017). A split-face, investigator blinded comparative study on the efficacy and safety of Q-switched Nd:YAG laser plus microneedling with vitamin C versus Q-switched Nd:YAG laser for the treatment of recalcitrant melasma. Journal of Cosmetic and Laser Therapy, 19(7), 383–390.

61. Wang, K., Jiang, H., Li, W., et al. (2018). Role of Vitamin C in Skin Diseases. Frontiers in Physiology, 9.

62. Wlaschek, M., Maity, P., Makrantonaki, E., et al. (2021). Connective Tissue and Fibroblast Senescence in Skin Aging. Journal of Investigative Dermatology, 141(4), 985–992.

63. Zeitter, S., Sikora, Z., Jahn, S., et al. (2014). Microneedling: Matching the results of medical needling and repetitive treatments to maximize potential for skin regeneration. Burns, 40(5), 966–973.