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An Oral Supplementation Based on Hydrolyzed Collagen and Vitamins Improves Skin Elasticity and Dermis Echogenicity: A Clinical Placebo-Controlled Study

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Abstract

The aim of this study was to evaluate the clinical efficacy of an oral supplementation based on hydrolyzed collagen and vitamins in the improvement of aged skin conditions using biophysical and skin imaging techniques. In this double-blind, placebo-controlled trials, 60 woman aged between 40-60 years were randomized to receive the product containing hydrolyzed collagen and vitamins (Group A) or the placebo (Group B), once daily for 90-days period. Skin elasticity, dermis echogenicity, hydration and, number of pores and wrinkles were measured before and at the end of the study. The results showed an improvement of the dermis echogenicity and skin elasticity, as well as a reduction of wrinkles and total amount of pores on the skin of the group A when compared with placebo group. Thus, it was concluded that oral supplementation under study present itself as a potential to act effectively on aged skin. Finally, the study contributes to the improvement of effective strategies to skin care beyond topical products use.

Keywords: Hydrolyzed collagen; Oral supplementation; Biophysical and skin imaging techniques; Skin elasticity; Clinical study

Introduction

Technological innovations in the area associated with the search for new methods to prevent and/or treat skin aging are emerging, and in this context, the concept of nutricosmetics appeared, which, by definition, are products for oral administration that have been specifically formulated for cosmetic improvements of the skin and appendices, and may be in the form of pills, food, liquids or tablets. These were created from the partnership between the cosmetic and food industries, and are also known as In & Out treatments and are mainly used for anti-aging proposes without invasive approaches [1,2]. However, according to the current resolutions, the nutricosmetics or oral supplementation, must also have studies and scientific evidence to prove its safety without medical supervision, which should not include health claims referring to the cure or prevention of any disease [3].

In addition, there is currently a strong tendency for facial treatments with oral supplementation for an improvement of the appearance as a whole. A healthy skin can be consequence of the substances that are consumed throughout the day, such as the ingestions of liquids, alimentary habits, solar exposure, age and use of oral supplementation, with vitamins and antioxidants. Thus, the approach of topical and oral treatments for skin benefits led to the creation of a new concept product called nutricosmetics [4] to complement the topical treatment. This way, products composed with collagen hydrolyzed and micronutrients have been proposed to oral supplementation, since they can act improving skin conditions, especially for mature skin consumers.

There are approximately 27 different types of collagen in the body, being the collagen type I the most abundant in the body [5,6]. In the skin, collagen types I and III represents, respectively, 85 to 90% and 8 to 11% of total collagen synthesized [7]. Collagen is essential for a proper maintenance of skin health, since both photoaging (caused by exposure to environmental factors as nutrition, ultraviolet radiation, etc, that leads to a degradation of collagen fibers and intrinsic aging (aging caused by the "chronological" natural effects of the metabolism), causes a decrease in the levels of this protein in the body [8], which leads to a decrease in the skin's thickness and firmness and loss of elasticity and hydration, that are mainly related with the reduction and modification of all skin elements: the fibroblasts become scarce, causing a slowdown in the collagen synthesis, which loses its regular and flexible appearance [8,9]. In addition, the muscles become flaccid, bone density is reduced and the joints and ligaments lose elasticity [10,11]. Vitamins A, C and E are among the most commonly studied. Vitamin E (tocopherol) is a fat-soluble nutrient with a primary function of protecting long-chain polyunsaturated fatty acids of cell membranes and lipoproteins against oxidation [12]. As for the vitamin C or L-ascorbic acid, in addition to its great antioxidant potential. Vitamin A is essential, among other factors, to cell proliferation and differentiation [13,14]. Zinc has antioxidant protection both *in vivo* and *in vitro*, and these actions can be directly related to the prevention of premature skin aging [15,16].

There are recent studies related with oral supplementation of hydrolyzed collagen in combination with vitamins, minerals or botanical extracts. Recently, an overview of the beneficial effects of Hydrolyzed Collagen was published, focusing on its effects on the skin [17]. The authors related studies concerning the bioavailability of hydrolyzed collagen, *in vitro* and *in vivo* scientific studies on the efficacy of collagen peptides, showing the benefits of collagen peptides on skin and the importance of controlled clinical trials to prove efficacy of this kind of products. However, double-blinded, randomized, placebo-controlled studies to evaluate the clinical benefits using biophysical and skin imaging techniques of oral supplementations with hydrolyzed collagen based products added or not with vitamins and others anti-aging ingredients are still scarce.

Finally, given the trends to complement the cosmetic use with oral supplementation and the benefits of hydrolyzed collagen and vitamins, a randomized and double-blind controlled clinical study is

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very important to assess the effectiveness of a daily intake of hydrolyzed collagen based product, enriched with vitamins A, C, E and zinc, when compared to placebo in the improvement and maintenance of the elasticity, density and firmness of the facial skin.

This way, the presented study contributes to a better understanding of the benefits of oral supplementation to skin, giving scientific evidence of the effectiveness of these products on the skin, benefiting consumers about the long-term clinical efficacy of functional food in elasticity and structural characteristics of the skin. In summary, it presents the clinical evaluation of the oral supplementation benefits on the skin employing advanced technologies of imaging analysis.

Material and Methods

Test product

The product under study is composed of a combination of Amino acids (Peptides of Hydrolyzed Collagen) and vitamin A, C, E, Zinc and excipients according to Table 1 and Table 2.

The presented treatment product contains a high concentration of the three main amino acids involved in the collagen synthesis: Proline, glycine and hidroxyproline. This combination of amino acids, when in association with the antioxidant complex of vitamins A, C, E and zinc, helps to promote a protection against the action of *Reactive Oxygen Species* (ROS), that causes oxidative stress, which are negatively correlated with the inflammation process and collagen synthesis [18]. Furthermore, the addition of Vitamin C is essential in the intracellular phase of collagen synthesis, promoting the hydroxylation of the amino acids proline and lysine into hydroxyproline and hydroxylysine, which results in the pro-collagen, a precursor molecule [19]. The placebo product also used in this study was composed of maltodextrin (carbohydrate from enzymatic conversion of corn starch) and excipients, which is a classic protocol for this type of clinical studies, as it does not affect directly the skin physiology [20].

Study design

The study was carried out as a monocentric, double-blinded, randomized, placebo-controlled study on the effects of an oral supplementation based on hydrolyzed collagen and vitamins on skin elasticity, dermis echogenicity and skin microrelief after 90 days of daily intake.

The study was approved by the Ethics Committee of the Faculty of Pharmaceutical Sciences of Ribeirão Preto/SP (CEP / FCFRP 339) and followed current Good Clinical Practice regulations. All test subjects received detailed information listing every relevant single parameter to the study and all the procedures involved. All subjects gave signed informed consent after written information and a possibility for further questioning.

Subjects

A total of 60 healthy female subjects were enrolled in the study: 30 subjects were randomized to each of 2 treatment groups to receive a daily dose of either 10 g of collagen and a mix of vitamins A, C, E and zinc or 10 g of the placebo (maltodextrin).

The products were taken orally by the subjects at home according to the instructions given by the investigator. The powder was to be dissolved in water or any other cold liquid. Prior to the beginning of the study and data acquisition, it was asked to the volunteers avoid the use of any anti-aging cosmetics as a preconditioning period during 7 days.

The study participants were also asked to not change their usual skin care routine or be part of any dermatological treatments on the test areas.

Inclusion criteria

The inclusion criteria were as follows: healthy females ranging in age from 40 to 60 years (homogeneous distribution between treatment groups); phototype II-IV (Fitzpatrick scale); general good health and mental condition; avoid sun exposure during the study period; personal informed consent to participate in the study; personal presence on the predefined days at the institute, and willingness and capability to follow the study rules and a fixed schedule, know that the data could be used to share the project. It was also instructed to the volunteers to not use other cosmetic products and to not change their alimentary habits during the study period.

Exclusion criteria

The exclusion criteria was as follows: any deviation from the above-mentioned inclusion criteria: pregnancy (or intention to become pregnant) or in period of breast feeding; skin diseases (e.g., atopic eczema, neurodermatitis or psoriasis) on the test areas or other dermatological disorders (e.g., scars, sunburn or moles), whose therapy could influence the results of the study, such as systemic steroids or antibiotics, steroids or local immunomodulatory topics three months prior to the study; smoking habit; severe disorders within 6 months prior to study start (e.g., cancer, acute cardiac and circularity disorders, severe diabetes, or alcohol or drug abuse); history of medical or cirurgical events that could significantly affect the outcome of the study, including any cardiovascular disease, skin disease, gastrointestinal diseases, indigestion, hypertension (>160/95 mm Hg on repeated measurements); participation in any other clinical study; medical treatments on the study area 30 days before the study start; use of tanning beds or self-tanning products a month before or during the study; any other condition that, in the opinion of the investigator, may interfere with the results or involves a risk to the subject.

Assessments

Test areas: The test areas were the frontal, periorbital and nasolabial regions of the face, being the periobital and nasolabial sides randomly chosen. On every measurement day, the subjects had to expose their uncovered test areas to the indoor climate conditions (21.5 ± 1°C and 50 ± 5% relative humidity) for 20 min.

Measurement times: There measures were made immediately before starting the product treatment (baseline values) and after 90 days (D90) of daily product intake.

Measurement of the stratum corneum water content: The water content of the stratum corneum was measured with a skin capacitance meter (Corneometer™CM 825, Courage and Khazaka Electronic GmbH, Cologne, Germany). The device determines the water content of the superficial epidermal layers down to a depth of about 0.1mm and expresses the values in arbitrary units. The average values of 5 measurements/ site were used in subsequent calculations [21].

Measurement of skin elasticity: For this evaluation, the equipment Cutometer® SEM 575 was utilized. It features a probe with negative pressure on the skin, and the captured light intensity is proportional to the skin penetration [22]. The Cutometer® analyses the mechanical parameters: Ua/Uf, the ratio of total retraction to total distension, called gross elasticity; Ur/Ue, net-elasticity of the skin without viscous deformation; Ur/Uf, the ratio of immediate retraction

Aspartic Acid	531 mg	Proline	1206 mg	Metionine	81 mg	Histidine	72 mg
Treonine	144 mg	Glycine	1574 mg	Isoleucine	117 mg	Lisine	378 mg
Serine	288 mg	Alanine	801 mg	Tirosine	18 mg	Arginine	819 mg
Glutamic Acid	1026 mg	Valine	216 mg	Fenilalanine	198 mg	Hidroxyproline	1161 mg

Table 1: Composition of amino acids presented in 10 g the treatment product under study.

Vitamin A (Retinyl Palmitate)	600 µg
Vitamin C (Sodium Ascorbate)	45 mg
Vitamin E (Tocopheryl Acetate)	10 mg
Zinc (Zinc Sulfate Monohydrate)	7 mg

Table 2: Composition of other active ingredients presented in 10 g of the treatment product.

to total distension, called biological elasticity; and Uv/Ue, the ratio of viscoelastic to elastic distension [23]. The measurement of each test area was repeated 3 times. The R5 value (Ur/Ue, immediate recovery/elastic deformation) was utilized as it is proven to be the most suitable in detecting age-related skin alterations [24].

Measurement of skin by high resolution photography: The Visioface® digital photography imaging system (Courage and Khazaka) was utilized for the evaluation of facial skin, consisting of a cabin attached to a high resolution digital camera (10 megapixels) and 200 white LED. This apparatus is connected to research software that enables evaluation of visible pores and wrinkles [25].

Measurement of dermis echogenicity: To the evaluation of the dermis echogenicity, 20 MHz ultra-sound equipment (Dermascan® C, Cortex Technology) was utilized. The ultrasonic wave (speed of 1,580 m/s) is partially reflected by the skin structure, giving rise to echoes of different amplitudes. To calculate the echogenicity, the number of pixels with low echogenicity is measured by means of the image analysis software and related to the total number of pixels [26].

Statistical analysis: Two-way ANOVA and Bonferroni post-test were used in this study. Statistical differences between placebo and collagen groups were ascertained by paired Student's T-tests for basal and T90 measurements for each parameter evaluated (GraphPad Software Inc., La Jolla, CA, USA). Differences were accepted as statistically significant at $p < 0.05$.

Results and Discussion

Measurement of the stratum corneum water content

After 90 days of treatment, the group receiving the product containing collagen and vitamins presented a significant effect in the stratum corneum water content parameter, but only in the frontal region, when compared to baseline values. However, this result is not significant when compared to placebo group. This hydration was in accordance with what was described by Proksch et al, where no statistical difference between the treatment group and placebo control at the baseline was observed [27]. Futhermore, Skovgaard et al, that studied an oral supplementation with similar composition, also observed a significant increase in hydration from baseline values when utilizing the treatment product, but it was not significant when compared to the placebo group [28].

Considering that Xhauflaire-Uhoda et al. demonstrated that the low increase of skin hydration can be related to the normal behavior of newly generated corneocytes from deeper skin layers [29], in this study, the presence of vitamin A in the product could to promote this feature. A study by Gianeti and Maia Campos undertaken at our research laboratory, using the same equipments, with a topical formulation containing an association of fat-soluble derivatives of vitamins A, C and E and botanical extracts showed, after a 30 day-period of treatment, a significant decrease of trans-epidermal Water Loss, increase of hydration and reduced wrinkles and skin roughness [30]. In addition, topical treatments with products containing peptides increased skin hydration [31] and also decrease the trans-epidermal water loss, improving skin barrier function.

These results suggest the importance of the association of both oral supplementation and cosmetic use for skin hydration and protection. Furthermore, the combined use of topical and oral peptides would enhance the effects, benefiting the skin appearance in many aspects.

Measurement of skin elasticity

According to the statistical analysis, only the group who received hydrolyzed collagen and vitamins product (A) presented significant differences in all evaluated parameters after 90 days of treatment when compared to the baseline values. This way, an increase of variables related to the immediate retraction, immediate distension and total distention ratio indicate an increase of elasticity and viscoelasticity of the skin. Furthermore, the significant increase of the immediate retraction / distension of the skin (Ur / Ue - R5 parameter) were obtained only on group A, when compared with baseline values and with the placebo group (Figure 1).

Borumand and Sibilla and Proksch et al [32,33] evaluated similar products and analyzed by the same equipments, observed a non-significant improvement of skin elasticity (R5 parameter) when compared to the placebo. In our study, the treatment with hydrolyzed collagen and vitamins product was effective, once an improvement of the skin elasticity was noted after 12 weeks of use, when compared to the placebo group. This result show the importance of the oral supplementation to improve skin age conditions once a loss of the structural support of the dermis is common in mature ages, leading to a less elastic skin that is also thinner and less able to resist to mechanical changes. With that, the present elastic fibers have the tendency to become deformed and less flexible. This decrease of collagen fibers in epithelial tissue is a result of the decreased fibroblasts metabolic activity, which are responsible for its synthesis [34]. So, the increase of skin elasticity parameters suggests an improvement of skin mechanical proprieties after the treatment with the oral supplementation under study.

Evaluation of skin by high resolution photography

Figure 2 shows a three-dimensional image shown where an evident reduction of wrinkles on the forehead to treatment with the product (collagen) is visible. Alterations of collagen and elastin can directly the affect wrinkle [35]. As the oral supplementation acts in the increase of collagen fibers and, along with the presence of vitamins C, E and zinc, with their antioxidant properties, effectiveness in the reduction of wrinkles and improving the appearance of the skin as a whole was noted [36]. Similar results in the reduction of wrinkles after the treatment with oral supplementation and analyzed with other techniques was related in the literature, demonstrating this way, the effectiveness of this type of products in the improvement skin appearance [32].

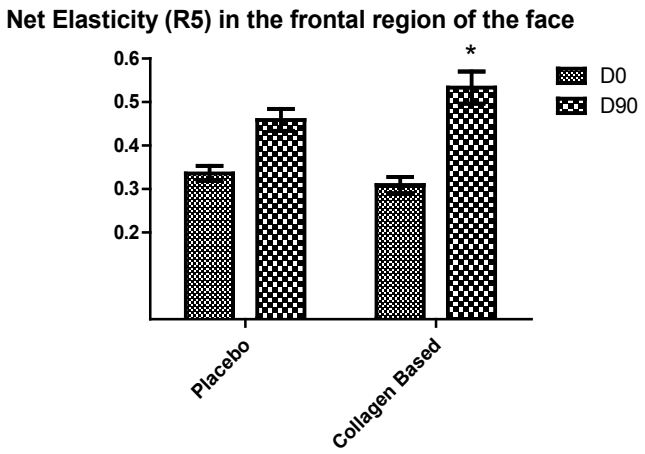

Figure 1: R5 Parameter (Net Elasticity – The closer to the value is to 1, the more elastic the skin) in the frontal region in groups A and B before (baseline) and after 90 days of treatment.

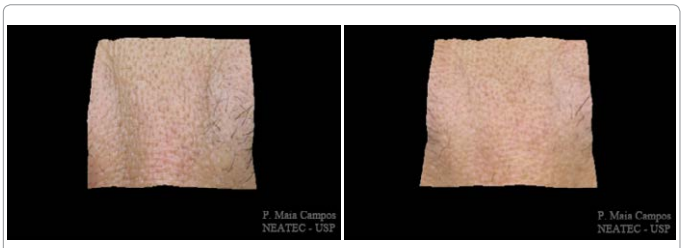

Figure 2: Three-dimensional images of the frontal area (glabella) at baseline and after 90 days of treatment with product A - collagen based, obtained with Visioface software Quick®.

In addition, 81% of the volunteers in Group A (hydrolyzed collagen based product) presented a reduction of the total number of pores and in 72% of volunteers in the Group B (placebo) presented an increase of the number of pores. These results are showed in the Figure 3 and Figure 4, which represent high resolution images of the reduction of large and small pores in the Collagen-based product volunteers group (collagen) and increase of pores in group B (placebo). Skin aging, and consequently, the loss of skin elasticity, leads to an increase in both pores size and numbers [37]. This way, the improvement of skin elasticity, as previously demonstrated, led to the reduction of skin pores size and number.

Measurement of dermis echogenicity

The high-frequency ultrasound provide measures of parameters related to the skin histology, analyzing the skin aging process and the echogenicity of the dermis - which is important as it varies with the chronological aging (intrinsic) and photoaging (extrinsic). This equipment also quantifies and qualifies the collagen and elastin fibers in the skin, being this way, an important contribution to clinical efficacy studies of dermocosmetic formulations [38].

This study showed an increase in the dermis echogenicity after 90 days of treatment with the hydrolyzed collagen based oral supplementation (Group A -Figure 5) when compared to the placebo treatment (Figure 6). This way, the product acted on the dermis, increasing of fibroblast density, enhancing the formation of collagen fibrils, and acting as a repairman of the present damages, slowing the chronological aging and photoaging process, increasing the echogenicity of the dermis and improving the skin density [39-41].

A high dermis echogenicity is related to a high content of collagen fibers, so the lower this ratio is, the more echogenic the skin. Thus, the treatment A has improved the dermis echogenicity when compared to placebo treatment in the frontal and nasolabial regions. The Figure 7 shows the Echogenicity Ratio of all three study regions. This parameter reflects the number of hypo echoic pixels / total number of pixels that increases during the aging process.

Skovgaard et al also studied an oral supplementation with a multifunctional product analyzed with different ultrasound equipment (DUBplus 20 - Taberna, Pro Medicum, AG, USA) and observed an increase of dermis thickness, suggesting that the treatment could stimulate the production of collagen in post-menopausal women [28]. In Summary, the treatment with the hydrolyzed collagen based product under study improved the echogenicity of the dermis (decreased echogenicity ratio), suggesting an increase of dermis density and this way, the firmness and elasticity of skin as well.

In addition, an improvement in skin elasticity was noted by significant alterations in the parameters related to the mechanical properties of the skin after 90 days-period of treatment with only hydrolyzed collagen-based product. The obtained high resolution

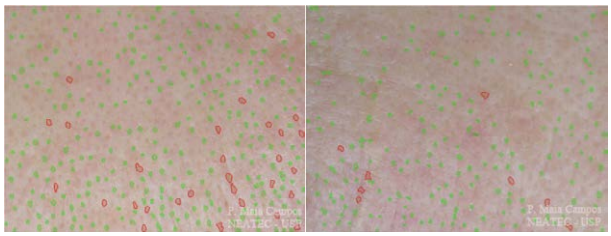

Figure 3: High resolution images of the frontal region of the face at baseline and after 90 days of treatment with product A - obtained at the Visioface Quick® software. Note the visible reduction in the number of pores.

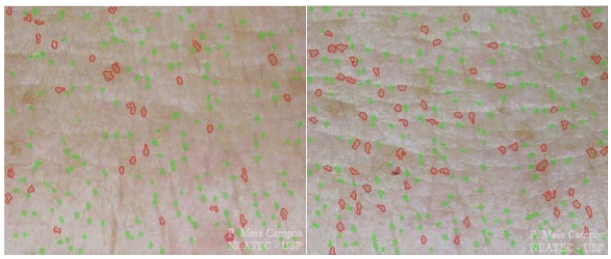

Figure 4: High resolution images of the frontal region of the face at baseline and after 90 days of treatment with product B - obtained at the Visioface Quick® software. Note the visible increase in the number of pores.

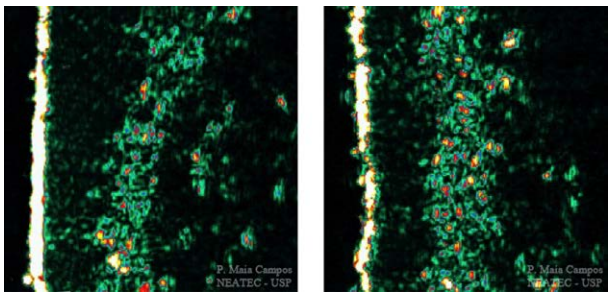

Figure 5: Dermis Echogenicity of a volunteer (Group A) before (baseline) and after 90 days of treatment. Echogenicity color scale: white > yellow > red > green > blue > black.

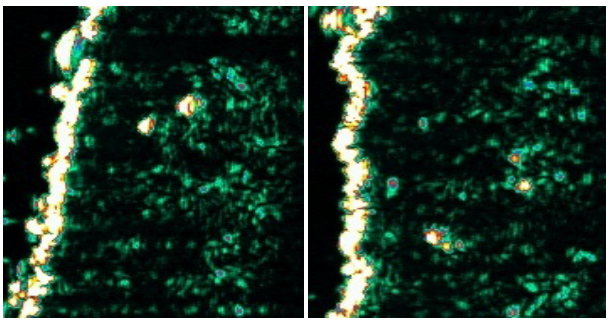

Figure 6: Dermis Echogenicity of a volunteer (Group B) before (baseline) and after 90 days of treatment. Echogenicity color scale: white > yellow > red > green > blue > black.

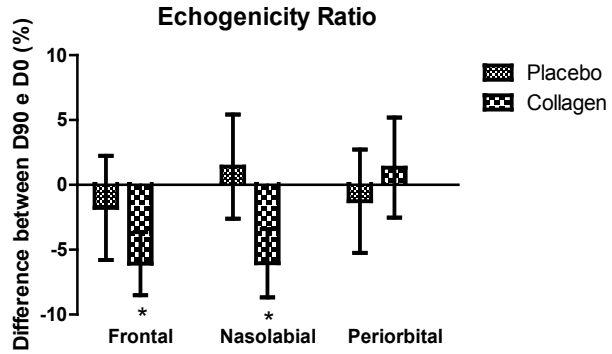

Figure 7: Difference (in percentage %) between the echogenicity ratio (number of hypo echoic pixels / total number of pixels) of the face regions of groups A (Hydrolyzed Collagen) and B (placebo), before (baseline) and after 90 days of treatment. * Significant difference from placebo ($p < 0.05$).

images showed a reduction in the depth of wrinkles and fine lines on the frontal and periorbital regions of the face after 90 days of treatment with product A. There was also a significant reduction in the total content of pores in volunteers who received treatment A (collagen), being more significant reduction in the frontal region (81%).

According to an overview of the beneficial effects of Hydrolyzed Collagen on the skin recently published [17], the results obtained in the present study is in accordance to what were reported on this review and showed significant effects in the improvement of skin hydration, elasticity, density and reduction of wrinkles and pores, evaluated by high-end imaging techniques in combination with the traditional biophysical techniques offering this way, real benefits to aged skin consumers.

Finally, the study described is an innovative proposal because it shows the importance of oral supplementation to improve skin elasticity and dermis echogenicity with hydrolyzed collagen and vitamins in combination evaluated by clinical studies using biophysical and skin imaging techniques.

Conclusion

Under the experimental conditions of this study, it was possible to conclude that the proposed hydrolyzed collagen based oral supplementation was effective in the improvement of skin elasticity and structure of the dermis. Moreover, the product had a positive effect reducing wrinkles and large pores after three months of use. Therefore, supplementation with a collagen based and vitamins A, C, E and zinc presents itself as a potential product to act effectively on the improvement on the aged skin conditions.

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