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High Serum Level of Matrix Metalloproteinase-1 (MMP-1) Correlates Positively with The Severity of Photoaging Facial Wrinkles

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ABSTRACT

Background: Matrix metalloproteinase-1 was chosen in this study because it is a subgroup of MMPs that play an essential role in the photoaging process of collagenases with degradation of collagen types 1 and 2 as a result of direct UVA and UVB exposure with significantly increased regulation of these exposures compared to other types of MMPs. The purpose of this study is to prove a positive correlation between high MMP-1 serum levels and the severity of facial wrinkles in photoaging subjects. ***Methods:*** Observational analytic study using a cross-sectional approach with comparative analysis aims to determine differences in the severity of facial wrinkles in patients experiencing Photoaging based on MMP-1 levels. Subjective clinical observation of wrinkles with Glogau score and objective use of the A-One-Facial Analyzer tool. Analyzing using SPSS 26. ***Results:*** 51 subjects were divided into two groups, 30 photoaging, and 21 non-photoaging. The results of the A-One-Facial Analyzer Photoaging group were 5.30 (4.70-6.50) and without Photoaging were 4.80 (4-5). MMP-1 serum levels in the Photoaging group median of 17.69 (9.78-84.07) pg./ml and non-photoaging group 11.56 (8.07-19.62) pg/ml ($p < 0.001$). Spearman Rho test between MMP-1 levels and wrinkles on the face obtained a moderate positive relationship with a correlation coefficient value (r) of 0, 5 and p-value <0.001. The result of the coefficient β was 41,5%, R-square 48%, and it was statistically significant with $p = 0.002$. ***Conclusion:*** High serum levels of matrix metalloproteinase -1 (MMP-1) have a positive correlation with the severity of facial skin wrinkles that experience Photoaging.

Keywords: facial wrinkles; matrix metalloproteinase -1 (MMP-1) serum levels; aging; young age; Photoaging

INTRODUCTION

Exposure to sunlight (ultraviolet rays [UV]) is a risk factor that plays an essential role in skin aging. The aging process caused primarily by sun exposure is known as photoaging. The effects of UV light are estimated to play a role in 90% of clinically visible skin aging [1]. Exposure to UVA and UVB rays can cause oxidative stress, which causes genetic damage, DNA, RNA, and chromosomes that run persistently, eventually increasing 3 MMPs (MMP-1, MMP-3, and MMP-9) in the skin with natural sources. It mainly originates from the epidermis. Skin damaged by chronic exposure to UV light expresses an increased 7 MMPs (MMP-1, MMP-2, MMP-3, MMP-9, MMP-11, MMP-17, and MMP-27), which are primarily derived from dermal fibroblasts [2–4]

Matrix metalloproteinase (MMP) or matrix is a structurally related group of proteolytic enzymes in the Metzincin clan. Matrix metalloproteinase contains zinc ions which are bound to three histidines in the active site which will secrete keratinocytes and dermal fibroblasts in response to various stimuli such as oxidative stress, UV radiation, and cytokines.

Matrix metalloproteinases mediate the degradation of various components extracellular matrix (ECMs). Until now there are 28 types of MMP that play an important role in pathophysiological processes including photoaging, wound healing, growth, skeletal remodeling, arthritis, inflammation, angiogenesis, and cancer[3].

Giving UVB in specific doses increased levels and activity of MMP-1 significantly compared to controls without UVB exposure[5]. The increase in MMP-1 levels was around 4.4 ± 0.2 times compared to skin that was not exposed to UV radiation [4]. Matrix metalloproteinase-1 was chosen in this study because it is a subgroup of MMPs that play a role important in the photoaging processing collagenase with degradation of collagen types 1 and 2 resulting from direct UVA and UVB exposure with significantly increased regulation of these exposures compared to other types of MMPs, and most markedly increased when skin severity is present [6–8].

Research in Indonesia regarding the correlation of serum MMP-1 levels with the severity of facial wrinkles experiencing photoaging is still limited, especially at Prof. Dr. IGN Ngoerah Denpasar, Bali. This hospital area was chosen because it is a Bali and Nusa Tenggara referral center with the most beach-visiting tourism destinations. Hence, this area's exposure to UVA and UVB makes more wrinkles possible.

METHOD

An observational analytic study using a cross-sectional approach with comparative analysis aims to determine differences in the severity of facial wrinkles in patients experiencing Photoaging based on MMP-1 levels.

The target population in this study were all men and women with wrinkles aged 20-45 years in Denpasar, Bali. Subjective clinical observation of wrinkles with Glogau score and objective use of the A-One-Facial Analyzer tool. The statistical analysis was conducted with the Statistical Package for The Social Sciences (SPSS) version 26.

RESULTS

This study was attended by 51 research subjects who met the eligibility criteria the results of the characteristics of the subjects in this study are presented in Table 1.

TABLE 1: Characteristics of Research Data.

Characteristics	Photoaging (n=30) (%)	Not Photoaging (n=21) (%)	p-value
Age (years) mean ± SB	28.43±5.79	29.71±4.95	0,414*
Gender			
Man	23 (76,67)	12 (57,14)	0,139**
Woman	7 (23,33)	9 (42.86)	
Profession			
Student	0	13 (61.90)	
Office employee	0	8 (38,10)	
Parking officers	9 (30.00)	0	
Gas station employee	8 (26,67)	0	
Street peddler	5 (16,67)	0	
Security guard	3 (10.00)	0	
Street sweeper	2 (6,67)	0	
Traffic police	2 (6,67)	0	
Motorcycle taxis driver	1 (3,33)	0	
Smoke			
Yes	2 (6,67)	3 (14,28)	0,368**
Not	28 (93,33)	18 (85,71)	
Smoking time (years)			
3 years	1 (3,33)	1 (4.76)	
4 years	0	1 (4.76)	
5 years	0	1 (4.76)	
10 years	1 (3,33)	0	
Number of cigarettes per day			
<5 sticks per day	1 (3,33)	1 (4.76)	0,622**
≥5 sticks per day	1 (3,33)	2 (9.52)	
Alcohol consumption	0 (0)	0 (0)	
Fitzpatrick skin type			
III	10 (33,33)	8 (38,10)	
IV	19 (63,33)	13 (61.90)	
V	1 (3,33)	0	
Glogau scale [median (min-max)]	3 (2-3)	2 (1-3)	
I	0	8 (38.09)	
II	6 (20.00)	10 (47,62)	
III	24 (80.00)	3 (14,28)	
A-One- Analyzer Facial Score [median(min-max)]	5.30 (4.70-6.50)	4.80 (4-5)	†<0,001***
Serum MMP-1 level [median (min-max)] pg/mL	17.69 (9.78-84.07)	11.56 (8.07-19.62)	†<0,001***

*Independent t-test; **Chi square test, ***Mann-Whitney; †significant.

The distribution of data in this study for serum MMP-1 levels was not normal so the difference test between photoaging and non-photoaging subjects was carried out using a non-parametric test, namely the Mann-Whitney test; the results were said to be significant if p <0.05. The results are presented in Table 2.

TABLE 2: Comparative Analysis of Serum MMP-1 Levels between Photoaging and Non-Photoaging Subjects.

Variable	MMP Level 1 Median (minimum-maximum) pg/mL	CI 95%	*p-value*
Photoaging (n=30)	17.69 (9.78-84.07)	*17.29-29.60*	*<0.001**
Not photoaging (n=21)	11.56 (8.07-19.62)	*11.58-13.18*	

*Significant if the value of p<0.05; analysis with the Mann-Whitney test;
MMP-1: Matrix Metalloproteinase-1.

In this study, because the data were not normally distributed, a correlation analysis was performed *with* the Spearman Rho test between serum MMP-1 levels and wrinkles on the face assessed based on the Glogau scale and A-One-Analyzer Facial. The results are presented in Table 3.

TABLE 3: Results of Correlation Analysis between Levels MMP-1 Serum with Severity of Facial Wrinkles.

Variable	MML-1 Serum level	
	Correlation Coefficient (r)	p-value
Glogau scale	0.513	<0.001*
A-One- Analyzer Facial score	0.505	<0.001*

*Significant p<0.05; correlation analysis with Spearman rho test;
MMP-1: Matrix Metalloproteinase-1 levels.

Based on the results of the correlation test, a moderate positive relationship was obtained with the correlation coefficient (r) value of 0.513 and p <0.001 between serum MMP-1 levels and the Glogau scale, as well as the results of the A-One-Analyzer Facial value with a correlation coefficient (r) which is 0.505 and a value of p <0.001 (Figure 1). This indicates that the higher serum MMP-1 level indicates an increase in facial wrinkles.

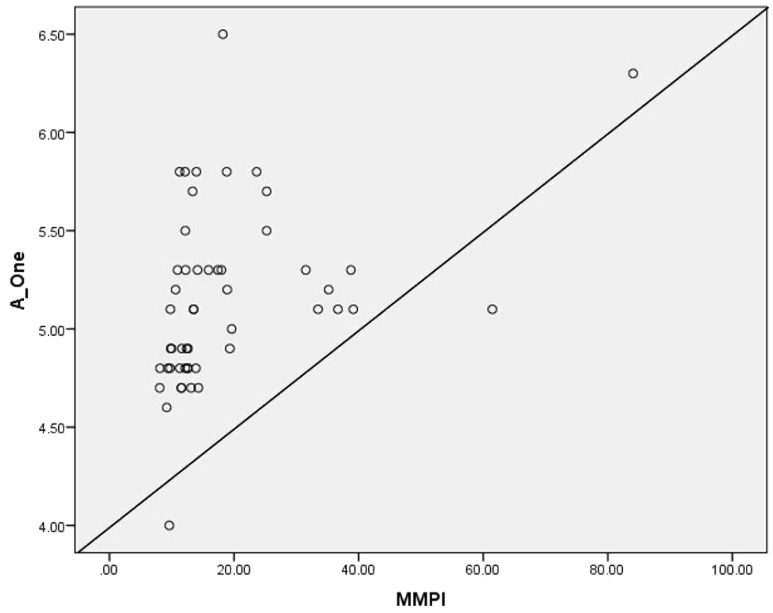

FIGURE 1: Scatter plot of A-One-Facial Analyzer on serum MMP-1 levels.

The data in this study were on a numerical scale, so a multivariate analysis was performed using linear regression analysis to determine whether serum MMP-1 levels would increase in photoaging, so a coefficient test was performed. Band R-Square (R2), whose results are shown in Table 3.

TABLE 4: Results of Linear Regression Multivariate Analysis Effect of Serum MMP-1 Levels on Subjects Experiencing Photoaging.

Variable	Serum MMP-1 levels					CI 95%
	B	t	coefficient	R-Square (R2)	p-value	
Photoaging	11,637	3,189	0.415	0.480	0.002*	4.30-18.97

*Significant p<0.05; linear regression analysis.

Coefficient results obtained 0.415 and statistically significant with p = 0.002, which means that any increase in serum MMP-1 levels will show an increase in photoaging of 41.5%. The R Square results determine the determination value obtained at 0.480, which means that the contribution of MMP-1 to photoaging is 48%. The rest is explained by other variables outside the model that are not examined.

In this study, more detailed observations were made regarding the results of smoking as seen from the Glogau scale, the A-One-Analyzer Facial score, and MMP-1 levels in the Photoaging and non-Photoaging groups are presented in Table 4.

TABLE 4: Correlation between smoking and serum MMP-1 levels with the severity of facial wrinkles.

Variable	Photoaging (n=2)	No Photoaging (n=3)	P-value
Glogau Scale [Median (Min-Max)]	3	3 (2-3)	
II	0	1	0,361*
III	2	2	
A-One- Analyzer Facial score [Median (Min-Max)]	5,9 (5,3-6,5)	4,9 (4,8-5,0)	0,083**
Serum MMP-1 level [median (min-max)] pg/mL	16,17 (14,14-18,21)	12,5 (9,81-19,62)	0,564**

*Chi Square test, ** Mann-Whitney test.

DISCUSSION

The results showed that the age distribution was normal and homogeneous, with the mean results in the photoaging group 28.43 ± 5.79 years and not photoaging 29.71 ± 4.95 not different. With age, a decrease in elastin, collagen, and hyaluronic acid causes skin strength and flexibility loss, resulting in wrinkles.[6,9] External factors are still the most influential factor in the process of wrinkling. These external factors can be exposure to UV rays, unhealthy lifestyles, environmental pollution, radiation, cigarette smoke, and stress.[10]

Sun exposure is the main contributor to photoaging by 80% compared to other extrinsic factors; therefore, extrinsic aging is also known as photoaging (Huang & Chien, 2020). The effect of photoaging will damage the connective tissue that will occur in the dermis layer in the form of biochemical reactions in the structure and organization of the extracellular matrix, mainly composed of collagen and elastin fibers. Elastin fibers are the main component of the dermis besides collagen. Elastin fibers affect the tension and elasticity of the skin. UV rays on the dermis will cause structural abnormalities and impair elastin function [8,11,12].

In this study, there was no significant difference between the sexes in the two groups with the result p = 0.139. These results are in accordance with research conducted by Latreille et al, 2012 which found 1655 men and 1264 women that there was no significant relationship between photoaging and gender [13]. In men, moisture, skin elasticity, and skin thickness are influenced by the hormone testosterone, while in women the most important role in regulating skin physiology, targeting keratocytes, fibroblasts, melanocytes, hair follicles, and sebaceous glands as well as increasing angiogenesis, wound healing, and an immune response is the hormone estrogen [14,15].

The most jobs in the photoaging group were parking attendants, with 9 people (30%), followed by gas station employees, with 8 people (26.67%), and street vendors, with 5 people (16.67%). In comparison, in the non-photoaging group, the most were students, with 13 people (61.90%) and 8 office employees (38.10%). Most jobs are outdoors with at least 120 minutes of sun exposure at 10.00-16.00 a day are known to make skin wrinkles and signs of photoaging.[11] Private employees and students are more active indoors with sun exposure <2 hours, so this exposure does not affect premature aging [8].

Smoking found no significant difference between the two groups. The results of this study are similar to those of Schnohr who stated that smoking does not have a significant effect on the occurrence of wrinkles at the age of 20-39 years.[16] Haruko found that in 650 subjects, 79% of people with white skin and 21% of black people aged 20-40 years who smoked ½ pack per day found no significant difference in the score of wrinkles between smokers and non-smokers in blacks, in whites, it was found that Daniel's average score did increase in smokers but after testing the analysis it turned out that there was no difference [17]

There was no difference in skin type in the photoaging and non-photoaging groups, Fitzpatrick skin type IV. Most cases of photoaging occur in European and North American populations with Fitzpatrick skin types I, II, and III reaching approximately 80% to 90%.[18] Ultraviolet B (UVB) rays affect the epidermis of dark skin by around 6%, while ultraviolet A (UVA) rays can affect the dermis by up to 18%. In fair skin, UVB rays affect the epidermis up to 30%, while UVA rays can affect the dermis up to 55%. An increase in the number of free radicals will lead to an increase in oxidative stress, which can damage cellular components, causing premature skin aging [11,19]. Fitzpatrick IV skin type in Asian countries has a skin type with a lower incidence of skin cancer due to photoaging compared to skin types in Europe and America [20].

Results A-One-Analyzer Facial score with abnormal data so that it uses the median value (minimum-maximum) with the results obtained in the photoaging group is 5.30 (4.70-6.50), while in non-photoaging 4.80 (4-5). Research using the A-One-Analyzer Facial score tool has also been carried out by Kawilarang, (2020), which states that the limit of wrinkle assessment in photoaging with a cut point is 4.7 [21]. Objectively the assessment of premature aging can be evaluated using the A One Smart Skin Analyzer score tool, which is a tool for analyzing skin using measurement methods with scanners and sensors. According to the production site for the A-One Smart Skin Analyzer score, namely Biomteck from Korea, it is stated on the packaging of this product that it is known to have passed clinical trials with a high sensitivity of 98% and a specificity of 99%.[22]

The results of the Glogau scale were obtained for photoaging, none of which had a value of 1 because exposure to high solar radiation made facial wrinkles increase. The Glogau scale appears at the age of 20-30 years with the characteristics of mild pigmentation changes, no keratosis, and minimal wrinkles.

In the non-photoaging group, 3 subjects (14.28) were already on the Glagau III scale. However, after the A One Smart Skin Analyzer score was performed, the photoaging group's median threshold remained the same. This could be due to intrinsic and other extrinsic factors needing to be examined in this study. Intrinsic factors occur as a natural process, influenced by genetics, hormones, and race. Other extrinsic factors include pollution, smoking or nicotine, and lifestyle (consuming alcohol) [1]. Internet-based cross-sectional survey analysis of more than 3,000 women from the United States (US), Australia, and Canada showed a significant association between facial aging with smoking and alcohol [23].

The median serum MMP-1 level in the photoaging group was 17.69 (9.78-84.07) pg/ml, while in the non-photoaging group, it was 11.56 (8.07-19.62) pg/ml. This study is not much different from that conducted by Amer, which found MMP-1 levels in photoaging with an average of 24.45 ± 1.2, while in non-photoaging subjects, it was 10.79 ± 1.4.[24] This is to Park's research, which states a difference between levels in photoaging with an average of 21.17 ± 3.62 and non-photoaging subjects 12.19 ± 2.83, one-way ANOVA test p 0.02.

The high levels of serum MMP-1 between photoaging and non-photoaging group subjects indicate that UV exposure can cause oxidative stress which causes persistent genetic, DNA, RNA, and chromosomal damage causing the formation of ROS, which can then trigger the upregulation of MMP-1. Increased MMP-1 causes degradation of ECM components resulting in decreased collagen production and procollagen biosynthesis. MMP-1 regulation is one strategy to prevent skin damage from sunlight. The development of anti-aging therapy modalities targeting MMP-1 is considered promising because of its ability to inhibit MMP-1 expression and activity, which can prevent photoaging. Matrix metalloproteinase-1 plays a role important in the photoaging process collagenase with degradation of collagen types 1 and 2 as a result of direct UVA and UVB exposure with significantly increased regulation of these exposures compared to other types of MMPs [11,25].

In addition to MMP-1, which response to UV A and UV B rays, MMP-13 is expressed but in a low amount. Collagenase-13 (MMP-13) expression was documented initially in human breast cancer, and MMP-13 favors type II collagen. In normal physiology, MMP-13 is abundantly expressed in developing bone and cartilage.

In addition, MMP-13 is expressed during many pathological conditions associated with excessive extracellular matrix (ECM) degradation, such as osteoarthritis cartilage, oral mucosal epithelium during chronic inflammation, and odontogenic keratocyst. Under normal conditions, the degradation and synthesis of ECM components are balanced so that collagenase is expressed at deficient levels. However, its production and activation are rapidly induced when active tissue remodeling is required.[2,3,26]

Collagenase-1 (MMP-1), collagenase-2 (MMP-8), and collagenase-3 (MMP-13) comprise a subfamily of collagenases capable of initiating the degradation of native fibrillar collagen types I, II, III, V, and IX. Collagenase-1 is most effective at breaking down type III collagen. Matrix Metalloproteinase-1 appears to be constitutively synthesized and secreted by fibroblasts and macrophages and is the collagenase most frequently associated with normal tissue remodeling. Matrix Metalloproteinase-1currently shown to be produced by various other cells such as osteoblasts and odontoclasts [2,3,26].

The results showed a moderate positive correlation between serum MMP-1 levels and the severity of facial wrinkles, subjectively using the Glogau scale and the A-One-Analyzer Facial value. Serum MMP-1 levels were higher in aging smoker-face subjects at 9.45 ± 8.16 pg/mL compared to normal subjects at 3.78 ± 3.11 pg/mL.[27] The risk of skin aging severity also occurs around 4.4 ± 0.2 times compared to skin that is not the most extended UV radiation.[4] Aging is a biological process influenced by many intrinsic and extrinsic factors. Similar to other organs, human skin undergoes progressive functional decline due to the accumulation of molecular damage.[28]

The clinical signs of photoaging include deep wrinkles, lentigines, rhytides, telangiectasias, dark spots (freckles), dyspigmentation, and loss of skin elasticity [25]. Skin aging occurs due to changes in the dermis layer in the form of decreased production of sebum and sweat, resulting in increased water evaporation. This process reduces the number and size of collagen and elastin fibers so that the elasticity and elasticity of the skin decreases. The aging of the dermis layer results in atrophy and reduced capillary blood vessels in several places so that the skin looks paler and nerve endings become abnormal [4,29,30].

Skin elasticity often appears as wrinkles due to damage to cell structures basal and degradation of the protein matrix. Collagen has a close relationship with skin elasticity. Procollagen type 1 and ECM are often decomposed, and elastin expression is often inhibited by matrix metalloproteinases (MMPs), which will induce activating protein 1(AP-1), a transcription factor, MMP-1 which is known to degrade collagen.[2,24] Research conducted by Mossback observed biological changes in the protein matrix components of aging skin often induced by ROS [31] The free radical theory continues to develop and has been proven through various animal experiments, showing that naturally, there are compounds that can prevent or slow down damage due to the aging process called antioxidants.[32,33]

The contribution of MMP-1 to photoaging is 48% with controlled research subject data characteristics, namely the results of age, sex, smoking, duration of smoking, number of cigarettes per day, and alcohol consumption obtained did not differ between subjects in the photoaging and non-photoaging groups. Jin's study (2004) showed that only 58% of MMP-1 levels could identify disturbances due to photoaging.[34] In contrast, in animal studies, mice found that MMP-1 levels affected photoaging by 46%.[24]

MMP-1 levels were the first type of matrix to increase compared to the other 2 types, namely MMP-3 and MMP-9, due to exposure to UV light. The transcription factor AP-1 tightly regulates these three MMPs, rapidly induced and activated by UV radiation in human skin. UV radiation causes the turnover of dermal collagen through two main pathways: 1) stimulation of collagen breakdown, resulting in fragmented and disorganized collagen, and 2) inhibition of procollagen biosynthesis, resulting in loss of collagen content [19].

The dermis layer of MMP-1 mRNA can increase by 30-45%, while in the epidermal layer, an increase of 76-85% is obtained [12]. In vitro studies by administering isoflavones to human fibroblast cultures exposed to UVB have been shown to inhibit collagen degradation by reducing MMP-1 by 46% [35]. The dermis layer of MMP-1 mRNA can increase by 30-45%, while in the epidermal layer, it an increase of 76-85%.[12] In vitro studies by administering isoflavones to human fibroblast cultures exposed to UVB have been shown to inhibit collagen degradation by reducing MMP-1 by 46% [35].

Matrix Metalloproteinase-1 is an enzyme that induces photoaging and photocarcinogenesis through collagenolysis in the skin due to UV radiation. Matrix metalloproteinase-1 is considered a multifunctional molecule because it participates not only in the turnover of collagen fibrils in the extracellular space but also in the cleavage of some non-matrix substrates and cell surface molecules that suggest a role in the regulation of cellular behavior. Moreover, ample evidence indicates that MMP-1 plays an essential role in various physiological processes such as development, tissue morphogenesis, and wound repair.[34,36]

Many therapies inhibit MMP-1 indirectly by inhibiting the formation of ROS on the market, such as vitamins C and E, coenzyme Q10, ferulic acid, green tea, idebenone, pycnogenol, and silymarin.[37]. However, the use of antioxidant supplements orally, according to Zhang & Duan, 2018 does not provide a preventive effect on chronic skin damage. The results of research on experimental animals found that Galla Chinensis (GAC), Neonauclea reticulate Extract, a member of Rubiaceae, a flowering plant rich in flavonoids and has a high total phenolic content and a suitable inhibitor of ROS in cell cultures of human skin fibroblasts, Ixora parviflora, and Coffea arabica which may protect skin from sun damage by reducing UV-induced ROS production, a polyphenol-enriched member of the Rubiaceae family, also exhibits anti-photoaging and anti-aging activityMMP-1.[19,38–40]

The results of a study conducted on humans were conducted by Cho et al, 2009 which conducted 30 healthy female subjects over the age of 45 years by administering aloe vera gel orally with 2 different doses, namely 1,200 mg/day and 3,600 mg/day for 90 days later Skin samples taken before and after administration of aloe vera were measured for MMP-1 and it was found that in both groups there was a decrease in MMP-1 levels with $p < 0.05$, although the mechanism by which aloe vera reduced MMP-1 was not known for certain.[41]

Topical retinoids can also reduce the amount of MMP-1 because retinoic acid compounds increase the number of collagen types I, III, and VII in the dermis and stimulate the normalization of elastic tissue organization and GAG deposition in the dermis.[42] Giving tranexamic acid cream with a concentration of 3%, 4%, and 5% can slow the formation of wrinkles and reduce levels of MMP-1.[43] Use a night cream containing AHA, BHA, retinol, vitamin A, a combination of niacinamide, resveratrol, and hexylresorcinol, and a day cream containing SPF to prevent photoaging.

Limitation in this study, the data distribution was not normal and not homogeneous, with an assessment limit using the median on the results of serum MMP-1 levels, the Glagou scale, and the results of the A-One-Smart Skin Analyzer score; this is a weakness in this study, although the results obtained it has been able to prove that there is a correlation between moderate positive correlation levels between high serum MMP-1 levels and the severity of facial skin wrinkles, an assessment has not been made of the limits of increased MMP-I levels in cases of photoaging, and no research has been conducted on the prevalence of increased MMP levels -1 serum against wrinkles. In addition, this study was only conducted at certain age limits and the data obtained was not normal and homogeneous.

CONCLUSION

High serum levels of matrix metalloproteinase -1 (MMP-1) positively correlate with the severity of facial skin wrinkles that experience photoaging.

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