Glycative Stress Research

Online edition : ISSN 2188-3610
Print edition : ISSN 2188-3602
Received : September 27, 2021
Accepted : December 21, 2021
Published online : December 31, 2021
doi:10.24659/gsr.8.4_190

Original article

Glycation and metabolic syndrome in the skin premature aging

Jana Janovska [1)], Claude Dalle [2)], Julija Voicehovska [3)]

1) Riga Stradins University, Department of Internal Disease, Riga, Latvia
2) World Society Interdisciplinary Anti-Aging Medicine, Paris, France
3) Riga Stradins University, Department of Internal Disease, Riga, Latvia

Abstract

***Purpose*:** In recent years, the role of advanced glycation end products (AGEs) in promoting and exacerbating metabolic and skin abnormalities has attracted much attention. In this study, we elucidated the relationship between AGE accumulation and skin characteristics, commonalities, and features in metabolic syndrome (MS) patients and controls.

***Methods*:** Caucasian male and female patients (n = 296) living in Riga, Latvia, divided into MS (n = 149) and non-MS (n = 147), were analyzed by skin lesion (epidermoid nigricans, seborrheic keratosis, actinic keratosis, age-related wrinkles, gravitational wrinkles, and facial telangiectasia). MS was diagnosed using IDF criteria. For glycative stress index, skin autofluorescence (SAF) was measured using AGE Reader, and skin AGE accumulation was evaluated. Skin findings were assessed using Dermatoscopy Dermlite for facial teleangiectasia, dermatosis and dyspigmentation. Blood biochemical analysis included oxidative stress indices (glutathione: GSH, selenoprotein: Se, superoxide dismutase: SOD, glutathione peroxidase glutathione peroxidase: GPx, and malondialdehyde: MDA).

***Results*:** The MS group showed higher body mass index (BMI) ($p < 0.001$, Mann-Whitney test), higher triglyceride (TG) ($p < 0.001$, Mann-Whitney test), lower HDL-C ($p < 0.001$, Mann-Whitney test), and lower Vitamin D ($p = 0.05$ compared to the non-MS group. For inflammatory response and oxidative stress, the MS group showed higher C-reactive protein (CRP) ($p = 0.007$, Mann-Whitney test), higher MDA ($p = 0.006$, Mann-Whitney test), and significantly equal SOD ($p = 0.291$). SAF, an index of glycative stress, was significantly equal in the MS group ($p = 0.468$). Next, we conducted a Spearman rank correlation analysis between SAF and each item. Significant correlations were found for the following items: FPG: $r = 0.345$ ($p = 0.036$, n = 37), TC: $r = 0.328$ ($p = 0.023$, n = 48), HDL-C: $r = -0.399$ ($p = 0.019$, n = 34), CRP: $r = 0.372$ ($p = 0.028$, n = 37), and CRP: $r = 0.372$ ($p = 0.028$, n = 37). No significant correlations were found with other items.

Skin lesions were classified as seborrheic keratosis (n = 109), actinic keratosis (n = 25), acanthosis nigricans (n = 16), aging wrinkles (n = 126), gravity wrinkles (n = 34), facial telangiectasia (n = 242), and lentigo pigmentosa (n = 204). SAF was positively correlated with skin aging parameters of seborrheic keratosis and lentigo pigmentosa ($p < 0.05$) and associated with the severity of skin aging on the face using the skin aging index ($p < 0.05$). In skin biopsies, the expression of GLUT-1 was increased, accompanied by a decrease in the number of regulatory T cells.

***Conclusion*:** MS was associated with excess ROS and reduced antioxidant capacity. Accumulation of AGEs in the skin was strongly associated with clinical aging-related changes (seborrheic keratosis, telangiectasia, and skin wrinkles). The AGE accumulation was associated with inflammatory processes, indicating that SAF may be closely related to skin health.

***KEY WORDS*:** advanced glycation end products (AGEs), metabolic syndrome, oxidative stress, aging, premature skin aging.

Introduction.

Recently, the role of heredity and telomerase shortening in the aging process has been recognized [1, 2)]. Theories of biological aging are complicated and involve both internal and external factors. Theories of skin aging are cellular senescence, decreased cellular DNA repair and telomerase, point mutations, increased frequency of chromosomal aberrations, single gene mutations, oxidative stress and glycation. In recent years, the role of advanced glycation end products (AGEs) in promoting and exacerbating metabolic and skin abnormalities has received increasing attention.

AGEs are produced when reducing sugars are non-enzymatically bound to proteins and lipids. This process

Corresponding to: Jana Janovska, MD
Anti-Aging Institute, Baznīcas Street 18, Riga, LV-1010, Latvia
TEL: +371-25-41-8181 e-mail: j.a.janovska@gmail.com
Co-authors: Dalle C, contacts@drclaudedalle.com; Voicehovska J, dr.julia.v@gmail.com

is facilitated by the hyperglycemic and hyperlipidemic environment characteristic of many metabolic disorders, including diabetes, obesity, metabolic syndromes (MS), and their complications. In the skin, AGEs cause biological modifications such as activation of molecular synthesis in the extracellular matrix (ECM)[3] and matrix degradation (matrix metalloproteinase: MMP)[4]. This review presents the idea that AGEs encompass the causes and consequences of premature skin aging and represent a "common background" underlying skin pathophysiology and barrier changes[5,6].

The aim of this study was to clarify the relationship between AGE accumulation and skin characteristics, common features and characteristics in MS patients and controls in terms of glycative stress. Furthermore, accumulation of AGEs and skin characteristics in MS patients were examined and analyzed in comparison with controls.

Subjects and Methods

In thisprospective study, we included male and female patients (n = 296) from our clinic living in Riga, Latvia, and performed an intergroup analysis of patients with and without MS. According to the International Diabetes Federation (IDF), the inclusion criteria for MS are presence of central obesity (defined by waist circumference with ethnic-specific values) plus one of the following four factors;

- Elevated triglycerides (TG) of 150 mg/dL (1.7 mmol/L) or more, or receiving specific treatment for this dyslipidemia.
- High-density lipoprotein cholesterol (HDL-C) (< 40 mg/dL [1.03 mmol/L] in men and < 50 mg/dL [1.29 mmol/L] in women) or receiving specific treatment for dyslipidemia.
- Elevated blood pressure (systolic pressure higher than 130 mmHg or diastolic pressure higher than 85 mmHg) or treatment for previously diagnosed hypertension.
- Fasting plasma glucose (FPG) of 100 mg/dL (5.6 mmol/L) or higher, or previously diagnosed type 2 diabetes mellitus (T2DM).

The patient's clinical examination, blood pressure and waist circumference were measured. Clinical examination of the skin was performed using dermatoscopy (Dermlite DL; Derma Medical Systems, Vienna, Austria)[7]. The detected skin manifestations (seborrheic keratosis, actinic keratosis, acanthosis nigricans, and facial telangiectasia) were divided into several subtypes (mild, expressive, and extreme expressive).

Blood biochemical analysis included cholesterol, HDL-C, LDL-C, vitamin D (Vit D) levels, C-reactive protein (CRP), and oxidative stress indices (glutathione: GSH, selenoprotein: Se, superoxide dismutase: SOD, glutathione peroxidase: GPx, malondialdehyde: MDA, and 4-hydroxy-2,3-trans-nonenal: HNE).

The AGE Reader™ (DiagnOptics B.V., Groningen, The Netherlands) was used to evaluate glycative stress[8]. The AGE Reader™ is a non-invasive device that measures tissue accumulation of AGEs in human skin on the forearm, and the results are expressed as values of skin autofluorescence (SAF) (Diagnoptics).

The Skin Aging Index (SAI) was evaluated. Tissue MDA and SOD was measured by using skin biopsy specimens from lesion and non-lesion area.

Statistical analysis

All data were calculated using SPSS 22 version. Descriptive statistics were used to show a normal distribution ($p > 0.05$). Means and standard deviations (SD) for age were calculated and shown in error bar graphs separately for men and women.

First, biserial correlation was calculated to determine if there was a correlation between the quantitative data and the dichotomous data (0 no, 1 yes). Since all the data involved in the data analysis by the Kolmogorov-Smirnov test fit a normal distribution ($p > 0.05$), parametric statistics were used to represent the descriptor statistics and the graphical data.

For quantitative data, groups were divided according to dichotomous data where binomial correlations were statistically significant and means and SD were calculated and displayed in error bar graphs; Pearson correlation between Age Reader™ and HDL was calculated, and statistically significant results were obtained and displayed in scatter plots.

For immunohistochemical analysis in 32 patients, parametric statistics were used for descriptor statistics and graphical data representation, as all data analysis by Kolmogorov-Smirnov test fitted a normal distribution ($p > 0.05$).

Ethical Standards

This study was conducted using existing materials that were not linked to personal information. Our study was designed in conformation to the Helsinki Declaration. The study protocol was approved by the Committee of Ethics, Riga Stradins University.

Results

MS group and glycative stress

Total 296 subjects (Age; 47.0 ± 11.2, BMI; 26.3 ± 4.8), of which 149 (50.4%) were MS (Age; 51.4 ± 9.8, BMI; 29.0 ± 4.2) and 147 (49.6%) were non-MS (Age; 42.4 ± 10.8, BMI; 23.6 ± 3.6).

Comparing the MS and non-MS groups, the MS group showed a significantly higher BMI ($p < 0.001$, ***Fig. 1-a***), higher FPG ($p < 0.001$, ***Fig. 1-b***), higher TC ($p < 0.001$, ***Fig. 1-c***), higher LDL-C ($p < 0.01$, ***Fig. 1-d***), not significantly lower HDL-C ($p = 0.702$, ***Fig. 1-e***), and higher TG ($p = 0.019$, ***Fig. 1-f***). Vit D was not significantly lower ($p = 0.063$, ***Fig. 1-g***).

In terms of inflammatory response and oxidative stress, CRP was significantly higher ($p = 0.007$, ***Fig. 2-a***), MDA was higher ($p = 0.006$, ***Fig. 2-b***), and SOD was not significantly different ($p = 0.292$, ***Fig. 2-c***) in the MS group, and there was no significant difference in Se between the two groups ($p = 0.382$, ***Fig. 2-d***).

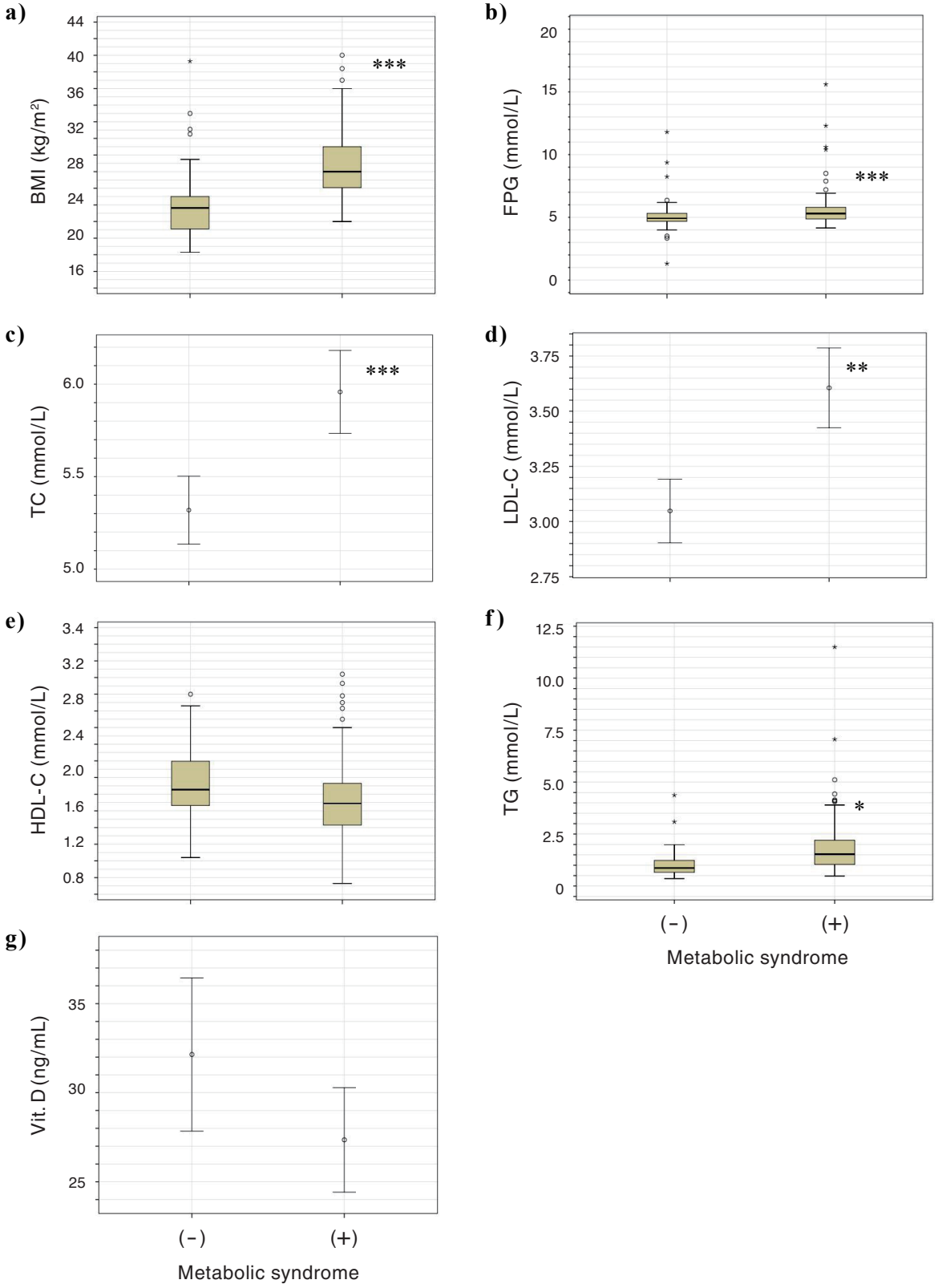

Fig. 1. **Comparison with and without metabolic syndrome (MS): BMI and blood chemistry.**

a) BMI, **b)** FPG, **c)** TC, **d)** LDL-C, **e)** HDL-C, **f)** TG, **g)** Vit. D. Results are expressed as mean ± 95% CI (box) and SD (bar). * $p < 0.05$, ** $p < 0.01$, *** $p < 0.001$, MS group (n = 149) vs non-MS group (n = 147) by Mann-Whitney test **(a**, **b**, **e**, **f)** or Student's t test **(c**, **d**, **g)**. BMI, body mass index; FPG, fasting plasma glucose; TC, total cholesterol; LDL-C, low-density lipoprotein-cholesterol; HDL-C, high-density lipoprotein cholesterol; TG, triglyceride; Vit. D, vitamin; CI, confidential interval; SD, standard deviation.

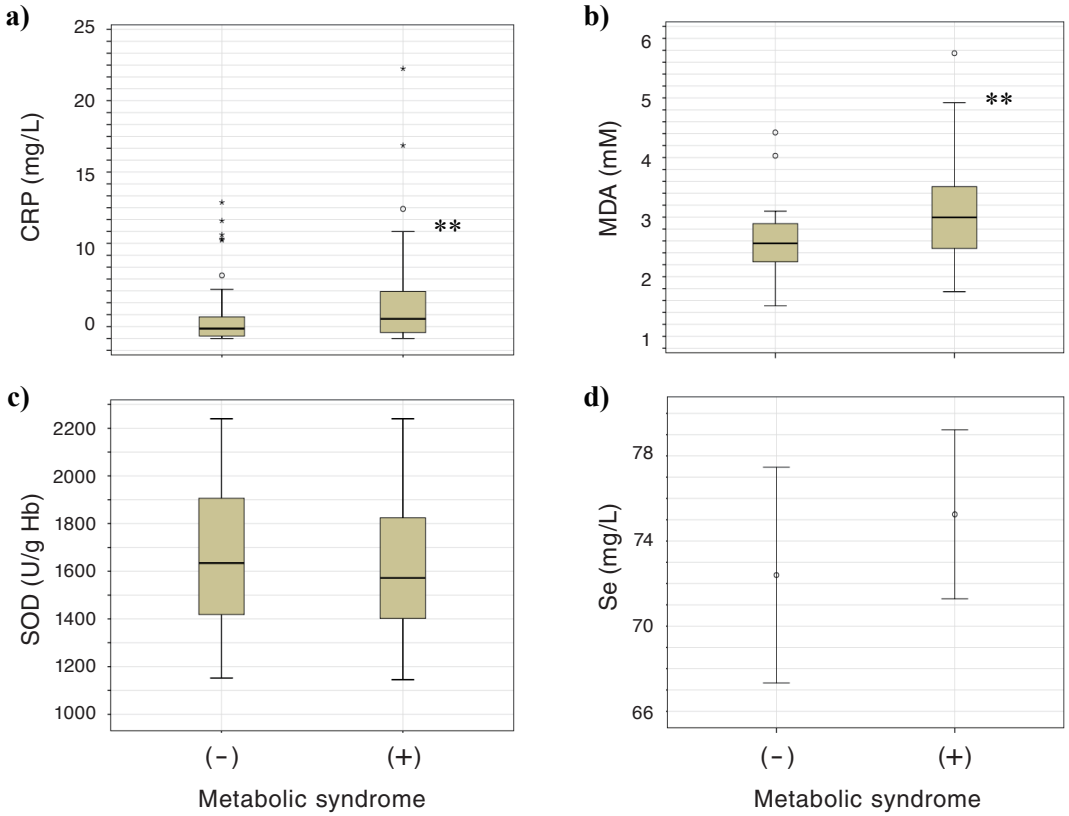

Fig. 2. **Comparison with and without metabolic syndrome (MS): Inflammation and oxidative stress.**

a) CRP, **b)** MDA, **c)** SOD, **d)** Se. Results are expressed as mean ± 95% CI (box) and SD (bar). ** $p < 0.01$, MS group (n = 149) vs non-MS group (n = 147) by Mann-Whitney test **(a, b, c)** or Student's t test **(d)**. CRP, C-reactive protein; MDA, malondialdehyde; SOD, superoxide dismutase; Se, selenoprotein: CI, confidential interval; SD, standard deviation.

SAF, an index of glycative stress, was significantly higher in the MS group ($p = 0.024$, ***Fig. 3-a***), and there was no difference in SAF between men and women ($p = 0.359$, ***Fig. 3-b***). Next, we conducted a Spearman rank correlation analysis between SAF and each item. Significant correlations were found for the following items: FPG: $r = 0.345$ ($p = 0.036$, n = 37, ***Fig. 4-a***), TC: $r = 0.328$ ($p = 0.023$, n = 48, ***Fig. 4-b***), HDL-C: $r = -0.399$ ($p = 0.019$, n = 34, ***Fig. 4-c***), CRP: $r = 0.372$ ($p = 0.028$, n = 37, ***Fig. 4-c***), and CRP: $r = 0.372$ ($p = 0.028$, n = 37, ***Fig. 4-d***). No significant correlations were found with other items.

MS and skin aging index (SAI)

The skin aging index, SAI, was significantly higher in the MS group ($p < 0.001$, ***Fig. 5-a***). SAI was also significantly correlated with SAF ($r = 0.203$, $p = 0.026$, ***Fig. 5-b***), Vit D ($r = -0.378$, $p < 0.001$, ***Fig. 5-c***), and systolic blood pressure ($r = 0.181$, $p = 0.102$, ***Fig. 5-d***).

There was no significant difference in GPx ($p = 0.208$, ***Fig. 6***) of the skin tissue between the two groups.

Analysis by skin lesions

The skin lesions were classified as seborrheic keratosis (n = 109), actinic keratosis (n = 25), acanthosis nigricans (n = 16), aging wrinkles (n = 126), gravity wrinkles (n = 34), and facial telangiectasia (n = 242).

The amounts of MDA and SOD in lesional and non-lesional areas are shown in ***Fig. 7-a, b***. MDA amount was higher in lesions of acanthosis nigricans ($p = 0.341$, Mann-Whitney test), but there were no differences in other parameters between lesions and non-lesions. SOD levels were higher in lesions for lentigo and actinic keratosis and higher in non-lesional areas for seborrheic keratosis. Lentigo pigmentation ($p = 0.332$, Mann-Whitney test), seborrheic keratosis ($p = 0.355$, Mann-Whitney test), actinic keratosis ($p = 0.464$, Mann-Whitney test).

When SAF was compared according to the presence or absence of lesions, it was not significantly higher in those with seborrheic keratosis ($r = -0.034$, $p = 0.588$, ***Fig. 8***). When compared by the presence of wrinkles, SAF was not significantly higher in those with mimetic wrinkles ($r = 0.091$, $p = 0.378$, ***Fig. 9-a***), age-related wrinkles ($r = 0.212$, $p = 0.001$, ***Fig. 9-b***), and gravity wrinkles ($r = 0.363$, $p < 0.001$, ***Fig. 9-c***).

FPG tended to increase with depth of wrinkles but it was not significant ($p = 0.721$, Kruskal-Wallis test, ***Fig. 10-a***). Analysis of skin biopsy tissues revealed a marked monocyte infiltration at the wrinkle formation site but the correlation with FPG was not significant ($p = 0.360$, Kruskal-Wallis test, ***Fig. 10-b***).

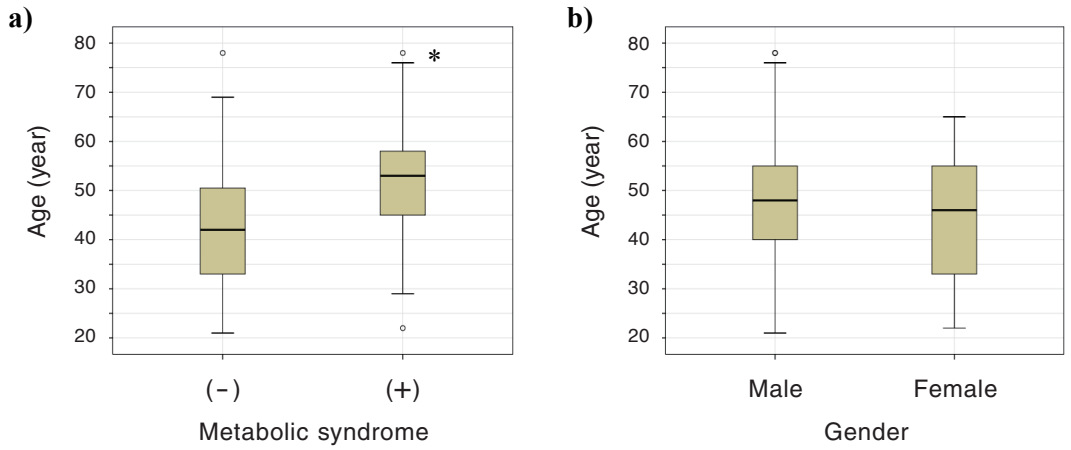

Fig. 3. **Age profile of the subjects.**

a) MS and non-MS, **b)** gender difference. Results are expressed as mean ± 95% CI (box) and SD (bar). * $p < 0.05$, MS group (n = 149) vs non-MS group (n = 147) by Mann-Whitney test. MS, metabolic syndrome; CI, confidential interval; SD, standard deviation.

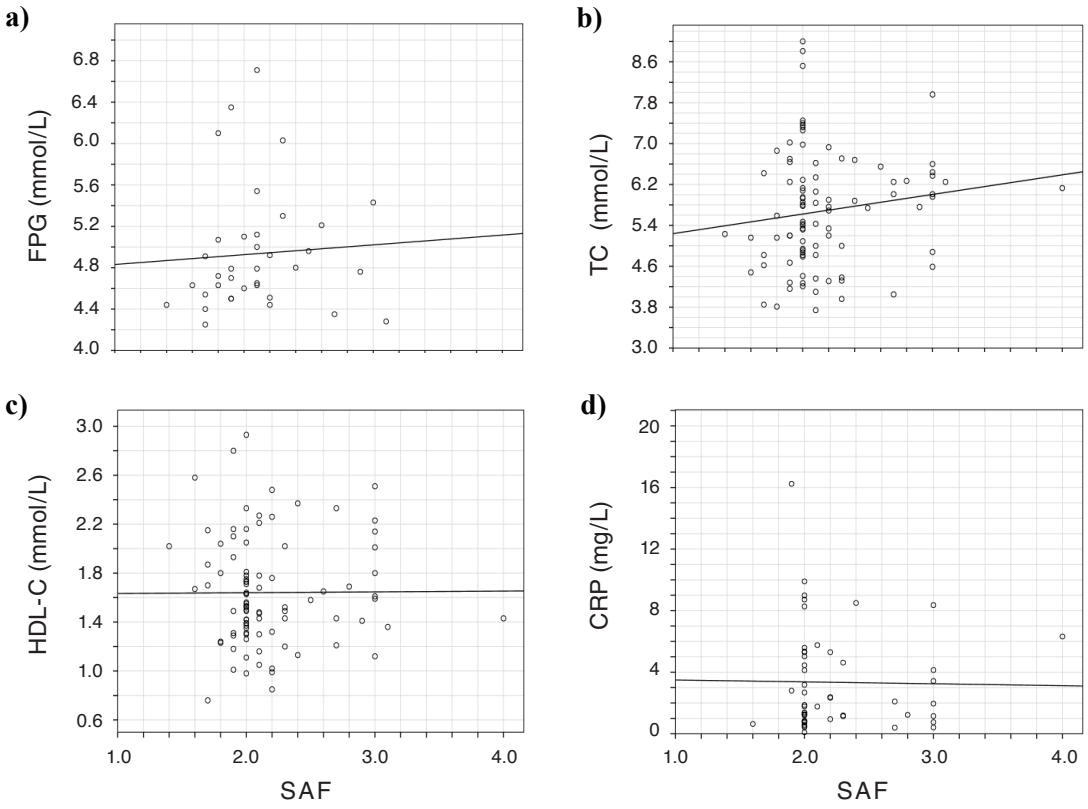

Fig. 4. **Relationship between SAF and blood chemistry data.**

a) FPG, **b)** TC, **c)** HDL-C, **d)** CRP. By Spearman rank correlation analysis. SAF, skin autofluorescence; FPG, fasting plasma glucose; TC, total cholesterol; HDL-C, high-density lipoprotein cholesterol; CRP, C-reactive protein.

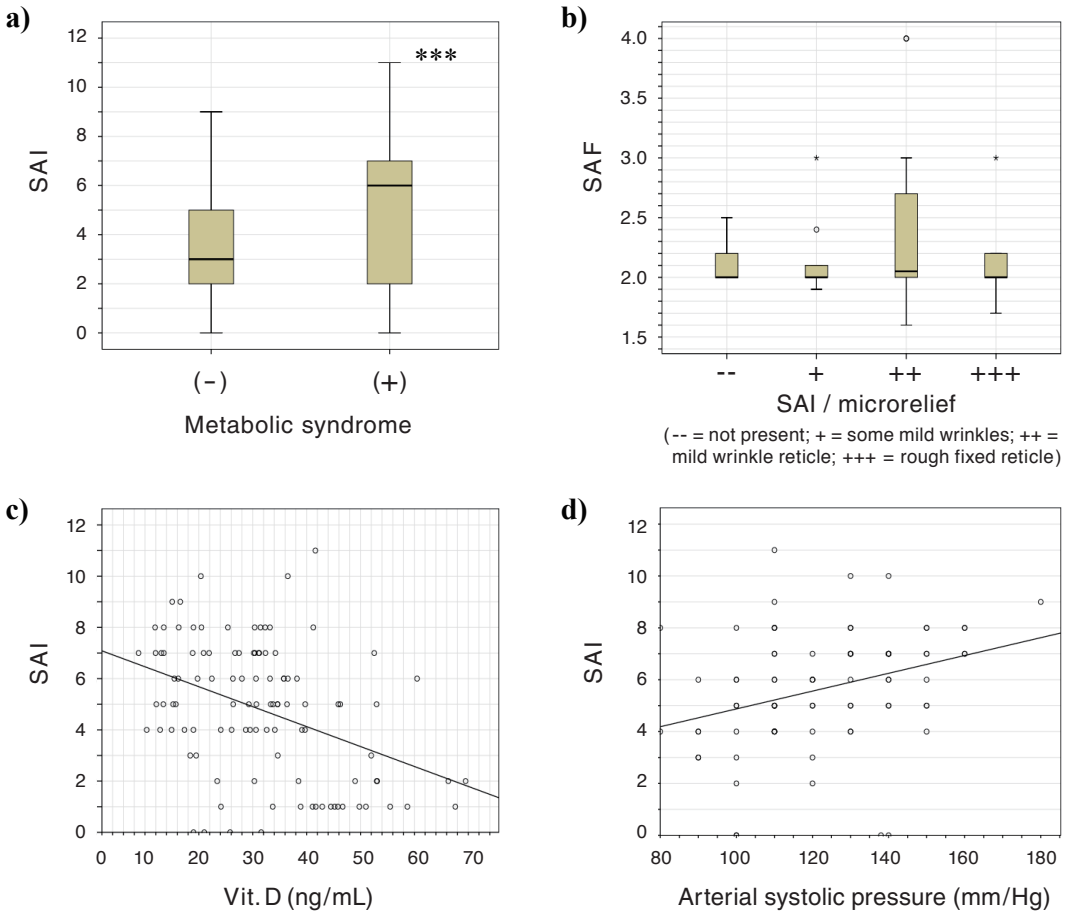

Fig. 5. **Relationship with Skin aging index (SAI).**

a) MS, **b)** SAF, **c)** Vit. D, **d)** CRP. Results are expressed as mean ± 95% CI (box) and SD (bar). *** $p < 0.001$, MS group (n = 149) vs non-MS group (n = 147) by Mann-Whitney test **(a)**. Spearman rank correlation analysis is conducted **(b, c, d)**. SAI (Y-axis in **a**, **c**, **d**), 0-2 = minimal, 2-8 = moderate, 8-15 = expressive; MS, metabolic syndrome; SAF, skin autofluorescence; Vit. D, vitamin; CRP, C-reactive protein; CI, confidential interval; SD, standard deviation.

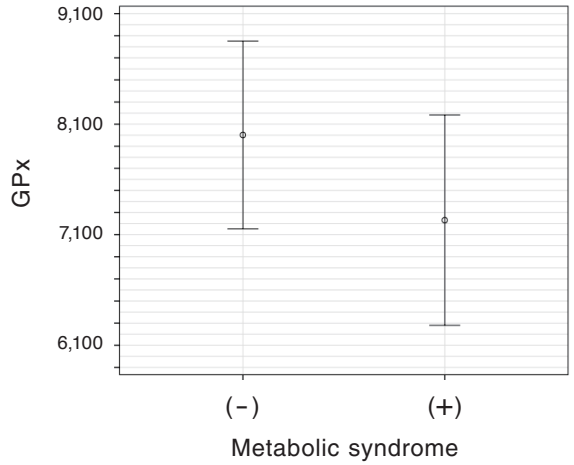

Fig. 6. **Comparison with and without metabolic syndrome (MS): GPx in the skin tissue.**

Results are expressed as mean ± SD (bar). MS group (n = 149) vs non-MS group (n = 147). GPx, glutathione peroxidase; SD, standard deviation.

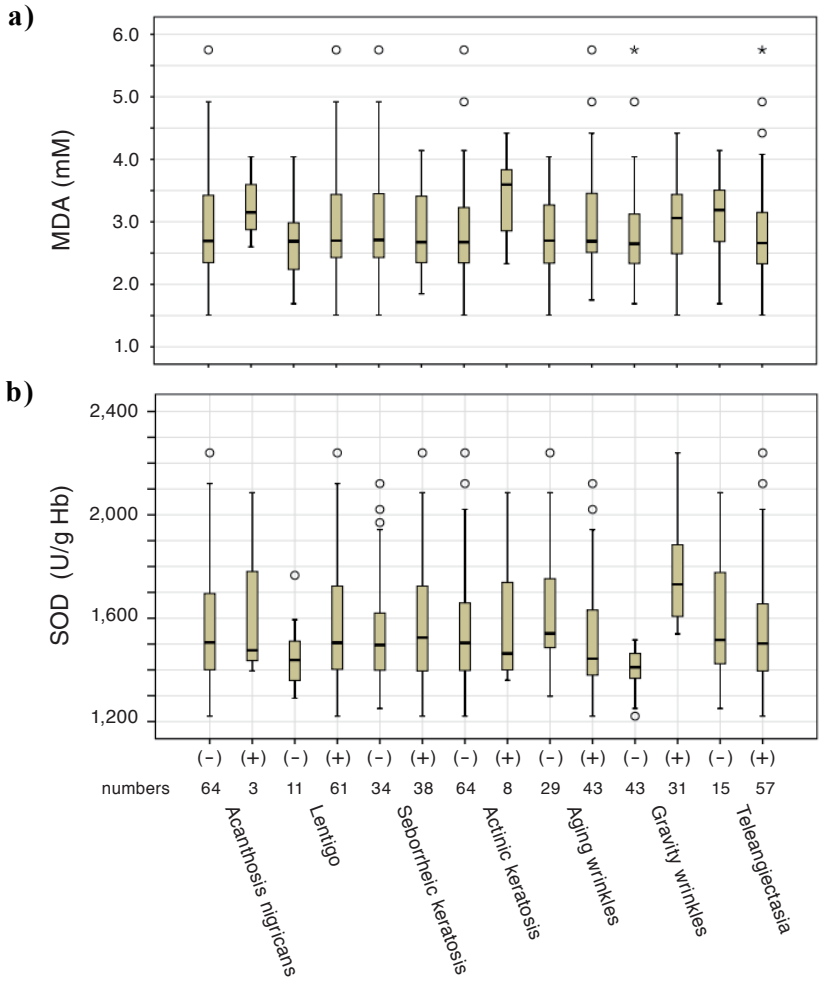

Fig. 7. **MDA and SOD in lesion and non-lesion areas**

a) MDA, **b)** SOD. Results are expressed as mean values of triplets or doublets. MDA, malondialdehyde; SOD, superoxide dismutase.

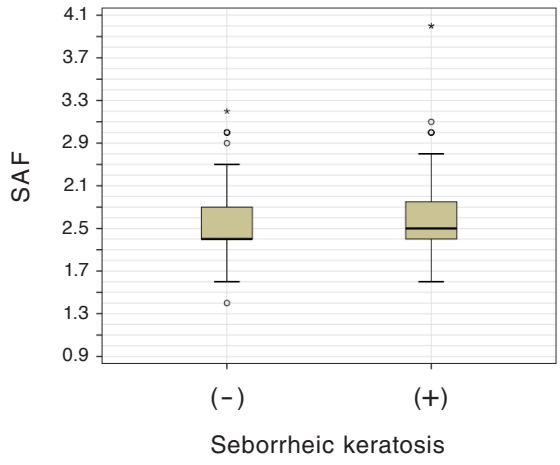

Fig. 8. **SAF and seborrheic keratosis.**

Results are expressed as mean ± 95% CI (box) and SD (bar), lesion (+); n = 63, lesion (–); n = 75. SAF, skin autofluorescence; CI, confidential interval; SD, standard deviation.

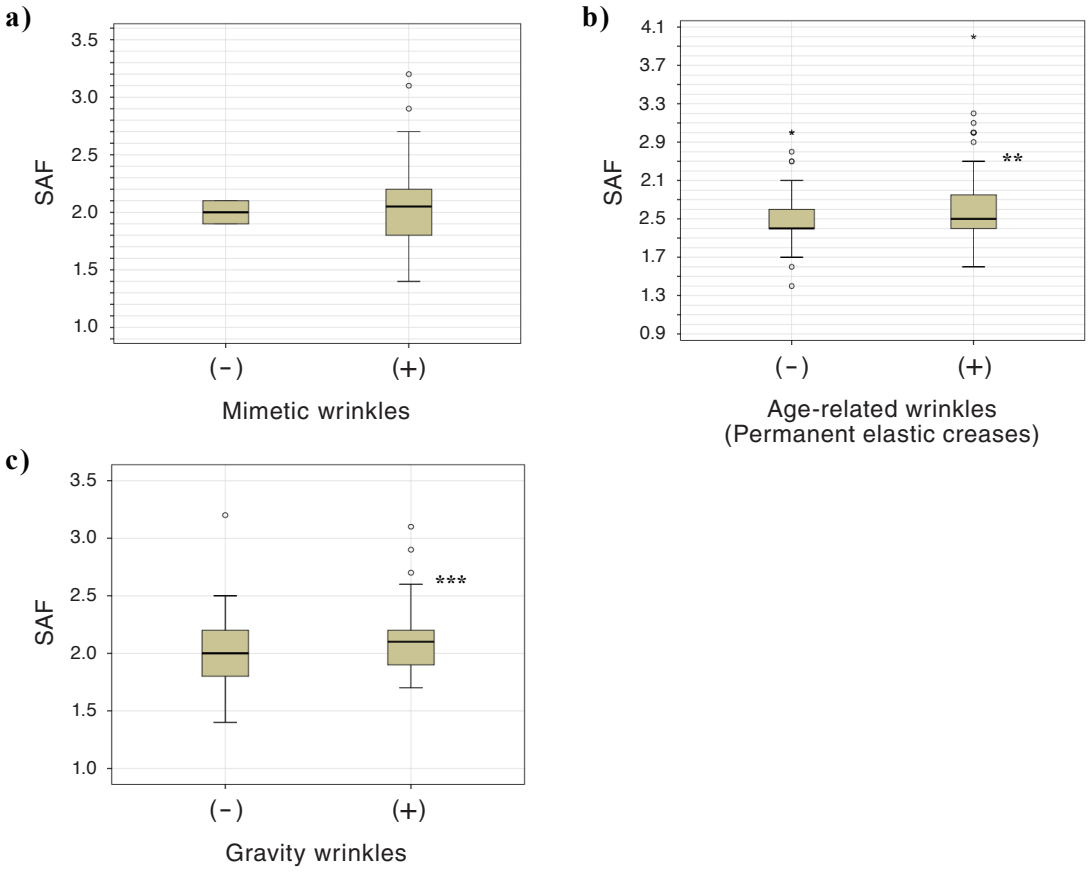

Fig. 9. **Relationship between Wrinkles and SAF.**

a) Mimetic wrinkles, **b)** Age-related wrinkles, **c)** Gravity wrinkles. Results are expressed as mean ± 95% CI (box) and SD (bar). **a)** lesion (+); n = 50, lesion (–); n = 2, **b)** lesion (+); n = 63, lesion (–); n = 74, **c)** lesion (+); n = 25, lesion (–); n = 27. ** $p < 0.01$, *** $p < 0.001$ by Spearman rank correlation analysis or Mann-Whitney test. SAF, skin autofluorescence; CI, confidential interval; SD, standard deviation.

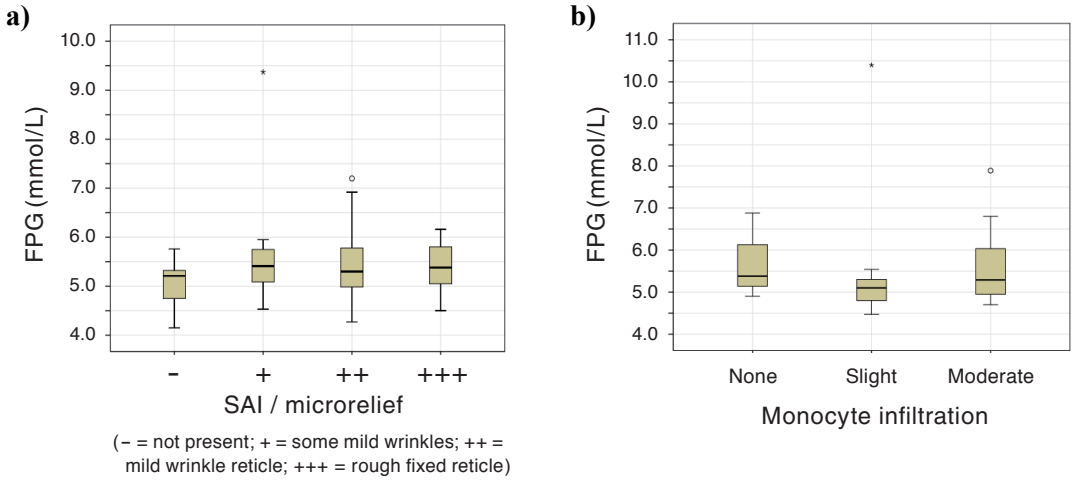

Fig. 10. **FPG and wrinkles / monocyte infiltration.**

a) Wrinkle depth, **b)** Monocyte infiltration in the wrinkle lesion. Results are expressed as mean ± 95% CI (box) and SD (bar), n = 160. FPG, fasting plasma glucose; SAI, Skin Aging Index; CI, confidential interval; SD, standard deviation.

Discussion

The present study showed the following;

- The glycative stress index and oxidative stress index were stronger in MS patients.
- SAF, an indicator of glycative stress, showed good key results regarding the correlation between endogenous skin aging factors and epigenetically induced reasons (exogenous aging) [9, 10].
- The accumulation of AGEs is associated with inflammatory processes *in vivo* (increased CRP and oxidative stress indicators).
- AGEs were associated with presence of MS, hypercholesterolemia, and increased BMI [11].
- The most frequent skin lesion that correlated with elevated SAF ($p < 0.05$) was acanthosis nigricans, especially in patients diagnosed with MS.
- The skin plays a major role in the metabolism and removal of reactive oxygen species (ROS), and MS is a factor in excess ROS and decreased antioxidant activity. This finding is consistent with previous reports [12].
- The accumulation of AGEs in the skin is more indicative of clinical age-related changes (seborrhea, actinic keratosis, telangiectasia, and deep wrinkles).

Aging is a complex, multifactorial process in which genetic, endogenous, and environmental factors play a significant role. Since the skin is the largest organ of the human body and is the boundary between the organism and the environment, it affects not only the appearance of youth but also various physiological functions. Aging skin exhibits impairments in skin permeability, angiogenesis, lipid and sweat production, immune function, and vitamin D synthesis, as well as the development of precancerous lesions and carcinogenesis [13]. The effect of glycoconjugates on aging skin is governed by the simple act of covalently cross-linking two collagen fibers, making the two not easily repairable.

In humans, with aging, the skin becomes drier and thinner, and photoaged spots become more prominent. These phenomena are influenced by epigenetic and genetic factors. There are two types of skin aging: endogenous (personal and genetic) and exogenous (environmental caused by ultraviolet radiation, radiation, exogenous substances, pollutant). One of these causes is premature aging due to accumulation of AGEs [14], which cause biological changes involving activation of molecular synthesis (extracellular matrix, cytokines, and enzymatic activation of matrix degradation, *i.e.*, metalloproteinases). The formation of AGEs is accelerated by ultraviolet (UV) exposure, oxygen, reactive oxygen species (ROS), transition metals with redox activity, and intermediate aldehydes. RAGE, receptor for AGEs, activates various molecular pathways in vivo and are involved in inflammation, immune response, cell proliferation, and gene expression. When AGEs are exposed to UVA radiation, ROS, *i.e.* superoxide anion, hydrogen peroxide, and hydroxyl radicals, are produced. These ROS stimulate nicotinamide adenine dinucleotide phosphate oxidase (NOX) to induce the production of superoxide anion and reduce the antioxidant defense system of cells [15].

MS and AGEs in skin lesion

The main features of MS are central obesity, glucose intolerance, dyslipidemia, and arterial hypertension. It is estimated that about 1/3 of the population is affected by this disease [16]. A variety of dermatological diseases have been associated with MS and/or its related conditions. MS also accelerates aging, at least in part, by causing damage to cardiovascular, renal, and other tissues, leading to pathological premature aging. In MS patients, there is chronic latent inflammation due to oxidative stress throughout the body, including the skin. This is a condition in which the net amount of reactive ROS exceeds the antioxidant capacity. Pro-inflammatory cytokines are released and a defensive inflammatory response in the skin ensues.

Excess ROS cause lipid peroxidation and oxidative damage to proteins and DNA. ROS affect the biosynthesis of collagen and increase inflammation. Specifically, the following reactions occur;

- Activation of MMPs.
- Activation of the aryl hydrocarbon receptor (AhR).
- Activation of transition metals by ROS and redox, which promotes the formation of AGEs [17].

The fat accumulation in MS associated with progressive insulin resistance triggers a cascade of hormonal changes, including effects on growth hormone. Hormones are self-regulating and synergistic. As a result, exacerbation of androgen-dependent skin diseases such as acne and male pattern baldness can be expected. Concurrently, inflammatory markers, *i.e.*, TNF-α, IL-17, IL-23, and oxidative stress may be involved in many autoimmune and inflammatory skin diseases [18]. Therefore, it is likely that impaired skin physiology may predispose to MS and vice versa [19].

In 2012, Nagel *et al.* investigated the relationship between the parameters of MS and skin cancer [20]. The results showed a positive relationship between malignant melanoma (MM) and elevated blood pressure in women. Furthermore, men with malignant melanoma tended to have a higher BMI. Women with squamous cell carcinoma/non-melanoma skin cancer tended to have increased FPG and TG. Also, the development of xanthomas and tendon xanthomas (although clearly not a proliferative tumor-like disease) is a very typical manifestation of congenital hyperlipoproteinemia [20].

MS and glycative stress

In recent years, the prevalence of glycative stress-induced diseases such as T2DM has been increasing, and it is easy to understand the relationship between T2DM and increased AGEs because of the marked increase in blood glucose concentration, but it should be noted that MS and dyslipidemia also are triggers for increased glycative stress. Sato K et al. reported that HFD -high-fat diettreatment suppressed GAPDH activity in rat liver, resulting in an increase in glyceraldehyde (GA) and methylglyoxal (MGO) [21]. GA is a highly reactive aldehyde that carbonylates surrounding substances and produces MGO. GA and MGO carbonylate and glycate proteins to produce AGEs. This is an important finding indicating that glycative stress is involved in HFD-

induced fatty liver. This is an important finding indicating that glycative stress is involved in HFD-induced fatty liver. AGEs increase the expression of CRP in hepatocytes and induce an inflammatory response [22]. AGEs promote the progression from simple fatty liver to non-alcoholic steatohepatitis (NASH) [23].

The mechanism by which HFD inhibits GAPDH is unknown. It has been shown that under conditions of high glycative stress, such as hyperglycemia, TCA cycling is impaired and fumaric acid increases, resulting in the formation of 2SC-GAPDH by succinylation of cysteine residue (-SH) of GAPDH, and thus GAPDH activity is decreased. We speculate that HFD may induce TCA cycle damage by a similar mechanism. MGO is conjugated to glutathione (GSH) and then metabolized to lactate by glyoxalase I & II. In the present data, GSH was also decreased in the MS group, suggesting that the activity of glyoxalase to degrade MGO may be decreased.

MDA is an oxidative stress product produced by the non-enzymatic oxidation of polyunsaturated fatty acids by ROS. In the present study, MDA was higher in the MS group, indicating that oxidative stress is stronger in MS. In addition, MDA tends to react with the sulfhydryl group of cysteine [24]. HFD ingestion produces more MDA than MGO in the liver [25], which reacts with cysteine, reducing the amount of free cysteine. Since cysteine deficiency triggers a decrease in aldehyde trapping actions, the reaction of MGO and MDA with the cysteine residues (-SH) of SOD-1 and GPx-1 is enhanced, reducing enzyme activity without decreasing protein levels.

Glycative stress and age-related changes in the skin

More specifically, oxidative stress and inflammation are associated with MS, and consequently, ROS damage to DNA and mitochondrial function and hormonal dysregulation (including insulin resistance) are associated with the aging process. Glycation of collagen in the skin is thought to be related to both MS parameters and aging. AGEs form cross-links with collagen fiber bundles, inhibiting their mobility and reducing skin elasticity [26]. This phenomenon is more intense in diabetics and accelerates skin aging. Intrinsic factors such as the Maillard reaction and oxidative stress affect gene expression in fibroblasts, lowering levels of MMP inhibitors and increasing production of MMPs which degrade collagen [19].

It also causes changes in skin tissue. Previously, our research group looked into the tissue changes in the skin structure of MS patients and found a high incidence of clinical hyperpigmentation and telangiectasia. Furthermore, dermal elasticity, thickening of the spinous layer and basement membrane, spinousness, and mild T lymphocytic infiltration around capillaries were observed. The accumulation of Bcl-2, an anti-apoptotic protein, in the epidermis was more pronounced in MS patients, indicating that MS patients also induce various degenerative changes in skin tissue [27].

Conclusion

The skin plays a major role in the metabolism and removal of ROS, whereas MS is a risk factor for increased ROS and decreased antioxidant capacity. Accumulation of AGEs in the skin is associated with inflammatory processes in the body (increased CRP, oxidative stress parameters) and clinically manifests aging-related lesions (seborrheic keratosis, telangiectasia, skin wrinkles). SAF has been shown to have significance in relation to skin aesthetics, functionality, and health status.

Conflict of interest declaration

None to be noted.

Acknowledgements

An outline of this study was presented at the Anti-Aging Medicine World Conference (AMWC) 2017, May 5-8, 2017, Monte- Carlo, Monaco.

References

1) Arsenis NC, You T, Ogawa EF, et al. Physical activity and telomere length: Impact of aging and potential mechanisms of action. *Oncotarget*. 2017; 8: 45008-45019.
2) Saretzki G. Telomeres, telomerase and ageing. *SubcellBiochem*. 2018; 90: 221-308.
3) Serban AI, Stanca L, Geicu OI, et al. RAGE and TGF-β1 cross-talk regulate extracellular matrix turnover and cytokine synthesis in AGEs exposed fibroblast cells. *PLoS One*. 2016; 11(3): e0152376.
4) Zhang J, Yang C, Wang C, et al. AGE-induced keratinocyte MMP-9 expression is linked to TET2-mediated CpG demethylation. *Wound Repair Regen*. 2016; 24: 489-500.
5) Ichihashi M, Yagi M, Nomoto K, et al. Glycation stress and photo-aging in skin. *Anti-Aging Med*. 2011; 8: 23-29.
6) Gkogkolou P, BöhmM. Advanced glycation end products: Key players in skin aging? *Dermatoendocrinol*. 2012; 4: 259-270.
7) Zaballos P, Blazquez S, Puig S, et al. Dermoscopic pattern of intermediate stage in seborrhoeic keratosis regressing to lichenoid keratosis: report of 24 cases. *Br J Dermatol*. 2007; 157: 266-272.
8) Meerwaldt R, Graaff R, Oomen PH, et al. Simple non-invasive assessment of advanced glycation endproduct accumulation. *Diabetologia*. 2004; 47: 1324-1330.
9) Nomoto K, Yagi M, Alita S, et al. A survey of fluorescence derived from advanced glycation end products in the skin of Japanese: Differences with age and measurement location. *Anti-Aging Med*. 2012; 9: 119-124.
10) Nomoto K, Yagi M, Alita S, et al. Skin accumulation of advanced glycation end products and lifestyle behaviors in Japanese. *Anti-Aging Med*. 2012; 9: 165-173.
11) Pietropaoli D, Monaco A, Pinto RD, et al. Advanced glycation end products: possible link between metabolic syndrome and periodontal diseases. *Int J Immunopathol Pharmacol*. 2012; 25: 9-17.
12) Corstjens H, Dicanio D, Muizzuddin N, et al. Glycation associated skin autofluorescence and skin elasticity are related to chronological age and body mass index of healthy subjects. *Exp Gerontol*. 2008; 43: 663-667.
13) Zoubulis CC, Makrantonaki E. Clinical aspects and molecular diagnostics of skin aging. *Clin Dermatol*. 2011; 29: 3-14.
14) Pageon H, Zucci H., Rousset F, et al. Skin aging by glycation: Lessons from the reconstructed skin model. *Clin Chem Lab Med*. 2014; 52: 169-174.
15) Ahmed N. Advanced glycation endproducts: Role in pathology of diabetic complications. *Diabetes Res Clin Pract*. 2005; 67: 3-21.
16) Roberts CK, Sindhu KK. Oxidative stress and metabolic syndrome. *Life Sci*. 2009; 84: 705-712.
17) Zhou SS, Zhou YM, Li D, et al. Dietary methyl-consuming compounds and metabolic syndrome. *Hypertens Res*. 2011; 34: 1239-1245.
18) Krueger JG. The immunologic basis for the treatment of psoriasis with new biologic agents. *J Am Acad Dermatol*. 2002; 46: 1-23.
19) Zhou SS, Li D, Zhou YM, et al. The skin function: A factor of anti-metabolic syndrome. *Diabetol Metab Syndr*. 2012; 4(1): 15.
20) Nagel G, Bjørge T, Stocks T, et al. Metabolic risk factors and skin cancer in the Metabolic Syndrome and Cancer Project (Me-Can). *Br J Dermatol*. 2012; 167: 59-67.
21) Zheng Y, Martin-Morales A, Wang J, et al. Phenethylamine in chlorella alleviates high-fat diet-induced mouse liver damage by regulating generation of methylglyoxal. *NPJ Sci Food*. 2021; 5(1): 22.
22) Takino J, Kobayashi Y, Takeuchi M. The formation of intracellular glyceraldehyde-derived advanced glycation end-products and cytotoxicity. *J Gastroenterol*. 2010; 45: 646-655.
23) Fernando DH, Forbes JM, Angus PW, et al. Development and progression of non-alcoholic fatty liver disease: The role of advanced glycation end products. *Int J Mol Sci*. 2019; 20(20): 5037
24) Arauz J, Ramos-Tovar E, Muriel P. Redox state and methods to evaluate oxidative stress in liver damage: From bench to bedside. *Ann Hepatol*. 2016; 15: 160-173.
25) García-Berumen CI, Ortiz-Avila O, Vargas-Vargas MA, et al. The severity of rat liver injury by fructose and high fat depends on the degree of respiratory dysfunction and oxidative stress induced in mitochondria. *Lipids Health Dis*. 2019; 18(1): 78.
26) Zouboulis CC, Makrantonaki E. Clinical aspects and molecular diagnostics of skin aging. *Clin Dermatol*. 2011; 29: 3-14.
27) Janovska J, Zavorins A, Voicehovska J, et al. Skin changes and peculiarities in patients with metabolic syndrome. *CBU Int Conf Proc*. 2013; 1: 264-271.