Potential Association of Type-2 Diabetes (T2D) and Advanced Glycation End Products (AGEs) measured by Skin Autofluorescence in Chinese Population

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Research Article

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Abstract

Background: Type-2 diabetes (T2D) has been associated with increased endogenous formation of advanced glycation end products (AGEs). Their accumulation in different tissues including articular collagen, skeletal and smooth vascular muscles, or glomerular basement membranes in T2D patients have been implicated.

Objective: To assess the potential association of T2D in skin ageing associated with AGEs in Chinese population.

Methods: A multicentre study was conducted in Chinese population of 560 subjects aged between 50 and 70 years who were evenly assigned in two groups of 280 each, paired by health status (healthy/diabetic), gender, and age group well balanced for hormonal replacement therapy/menopausal status, body mass index (BMI), smoking status and skin characteristics. Skin conditions were examined by a dermatologist and skin autofluorescence (SAF) a marker of AGEs measured by a validated non-invasive *in vivo* measurement technique.

Results: The results from this study confirmed the association of diabetes and skin ageing as increased AGEs accumulation were measured using SAF and contributed evidence on gender and ethnic origin on AGEs variations. This study opens the path of further investigation into the identification of significant effects of diabetes on major facial skin complexion parameters.

1. Introduction

Diabetes mellitus or Type 2 diabetes (T2D) is a metabolic disorder characterized by chronic hyperglycaemia [1]. Dermatological complications are common in diabetic subjects, with about 30% of patients experiencing cutaneous involvement such as acanthosis nigricans, necrobiosis lipoidica, diabetic dermopathy, etc. [2]. These complications could be a result of hyperglycaemia and decreased insulin or could be associated with specific chronic complications of the disease as well as antidiabetic drugs treatment or secondary endocrine and metabolic disorders [2, 3]. The disturbed epidermal barrier function in diabetic subjects frequently increases the susceptibility to bacterial and fungal infections, which could occur less frequently in healthy people. Specific skin disorders such as necrobiosis lipoidica diabeticorum, scleroderma adultorum, acanthosis nigricans, are the result of diabetic vasculopathy and neuropathy [3].

Higher perceived age on the face has also been associated with high serum glucose levels [4]. High levels of glucose in diabetes can react by nonenzymatic Maillard reactions with proteins to form unstable, highly reactive proteins with carbohydrate adduct [5, 6]. These products are termed advanced glycation end products (AGEs) and are known to crosslink collagen [7].

Although the AGEs formation is associated with normal ageing [8], their progression may be accelerated in diabetic subjects because of their elevated blood sugar [8, 9]. Furthermore, excessive AGEs are

associated with the pathogenesis of microvascular and macrovascular complications, which affect organs in the nervous system, the heart, the kidneys, and small blood vessels [10].

Several studies have demonstrated that elevated skin autofluorescence (SAF) reflects skin AGEs and can be used as biomarkers of diabetes [11, 12, 13, 14]. Additionally, SAF highly correlates with diabetic complications, and it is a predictive factor for diabetic retinopathy and nephropathy [13, 14, 15]. Both SAF and loss of skin elasticity increase with age, suggesting an implication of AGEs in the cutaneous alterations observed with ageing [16]. However, the direct contribution of glycation to the loss of skin elasticity is not yet clearly demonstrated.

In China, with the rapid economic growth and urbanization, lifestyle changed significantly. Over the past 40 years, the prevalence of diabetes in China has increased from less than 1 to 12.8% in 2018, and the prevalence of prediabetes is 35.2%, making it the country with the largest number of diabetes cases in the world [17]. Additionally, the national survey in China also showed that a large proportion of diabetes was undiagnosed and that patients with newly diagnosed diabetes accounted for 60% of the total diabetic population [18]. Consequently, it is striking that diabetic nephropathy among those with T2D has become one of the most important public health crises in China, and there is an urgent need to assess the epidemiological characteristics and risk factors of diabetic nephropathy in T2D in China to implement effective interventions [19].

Having specific and simpler methods such as SAF will be useful in measuring AGEs formation and its rapid progression due to elevated blood sugar levels in diabetic subjects to prevent further microvascular and macrovascular complications.

This is a report of the findings from a study, regarding the potential influence of T2D in dermatological complications and skin ageing associated with AGEs determined by SAF in a Chinese population.

2. Material And Methods

2.1 Subjects

A total of 560 participants (280 type-2 diabetic participants and 280 healthy participants) were recruited from 4 different cities in China (Beijing, Shanghai, Chengdu, and Guangzhou) for an epidemiological study assessing lifestyle parameters and demographic variables of patients with Type 2- diabetes (T2D) and the effect of those factors on skin complexion by measuring advanced glycation end products (AGEs) levels using skin autofluorescence (SAF).

All the diabetic participants had a history of T2D, meeting the criteria defined by the American Diabetes Association, fasting plasma glucose ³126 mg/dL (7.0 mmol/L) or 2-hour plasma glucose ³200 mg/dL (11.1 mmol/L) during oral glucose tolerance test or A1C ³6.5% (48 mmol/mol) or in a patient with classic symptoms of hyperglycaemia or hyperglycaemic crisis, a random plasma glucose ³200 mg/dL (11.1 mmol/L) [20]. The subjects were between 50-70 years of age, with body mass index (BMI) between 19

and 35. The study was approved by the local ethics committee. The informed consent form was written in Chinese (native language) and signed by each participant. The diabetic participants were matched with the healthy participants as per the following rules:

- 1:1 female to males
- 1:1 healthy to diabetic participants evenly distributed into 4 age groups (50-54, 55-59, 60-64, 65-70 years old)
- 140 participants from each site in China: Guangzhou, Beijing, Shanghai, Chengdu

Quality of life was assessed using the Chinese Quality of Life Instrument (ChQOL). According to Leung's validated method, the 13 items of the Quality-of-Life Questionnaire were gathered in 3 main domains (physical form, spirit, and emotion) and an overall score was calculated by adding the item scores from 0-100 points [21]. The same method was used to get the domain scores and overall scores.

2.2 Facial skin dermatological evaluation

Skin features were qualitatively assessed using standardized high-resolution digital photographs of the face of the participant (face and profile) and quantitatively assessed during the clinical evaluation by a dermatologist. Pigmentary spots and wrinkles were assessed on the face to evaluate skin photo-damage according to the grading of Chung for facial wrinkles severity and dyspigmentation [22]. The severity of the wrinkles was assigned grades 0-7, thus making an 8-point scale where 0 represents no wrinkles and 7 indicates severely wrinkled [22]. The grade of pigmentation used a 6-point scale method, with 0 representing no dyspigmentation and 5 representing severe dyspigmentation [22]. Skin slackening was assessed using Tsukahara's grading scores, 1-2 for slight, 3-4 for mild, 5-6 for moderate, 7-8 for severe, and 9-10 for very severe sagging [23]. The dark circles and bags under the eyes were also both scored on quantitative scales, with 1 for never, 2 for seldom, 3 for often, and 4 for always. Cutaneous manifestations of diabetes and skin phototype typing according to Fitzpatrick's scale were examined [5,24]. Higher scores denote worse skin conditions.

2.3 Quantification of AGEs in skin

SAF was examined on the inner forearm using the AGE Reader (DiagnOptics BV, The Netherlands) [14]. AGE Reader is a diagnostic device that measures the tissue accumulation of AGEs noninvasively using the fluorescence of ultraviolet light. Briefly, the skin was irradiated with a UV source (λ_{max} 350 nm) and the emitted fluorescence (λ_{em}) was measured between 420 and 600 nm. SAF was calculated by dividing the mean fluorescence intensity per nm (over the entire emission spectrum range 420 – 600 nm) by the average fluorescence per nm (in the range of 300 – 420 nm). The reflectance (RI) was determined from the spectra obtained during the skin measurement and those against the white standard, both after subtraction of the respective dark measurements. SAF was considered unreliable if RI was below 6%. Measurement was the mean of 3 measures per person.

2.4 Statistical analysis

The subjects were classified into 4 age groups (50-54, 55-59, 60-64, and 65-70). Age and health status influence was first analysed by ANOVA, and the difference between the age groups ranked after a Newman Keuls test. Health status, gender, and age group are categorical descriptive variables. Multiple linear regressions were used to determine the association of T2D and SAF with the descriptive variables mentioned above. Least square means was used to predict the behaviour of the variables; results were reported along with the significance levels. As the scales for overall severity of facial wrinkles and the presence of dyspigmentation were different for men and women, they were also analysed by gender in addition to a global test. Statistical analyses were performed with Statgraphics plus Centurion package and SAS version 9.

3. Results

3.1 Clinical characteristics

The clinical characteristics of the 560 (50–70 years old) included subjects are summarized in Table 1.

Table 1
Clinical characteristics of the two study groups according to health status

	HEALTHY	TYPE-2 DIABETES [a]
Number	280	280
Gender (male/female) [b]	140/140	140/140
Menopausal n - % (females)	109–77.8%	116–82.8%
Age (years ± SD)	59.53 ± 6.31	60.52 ± 6.59
BMI (kg/m^2 ± SD)	24.48 ± 3.14	24.50 ± 2.81
Hip to waist ratio (± SD)	1.12 ± 0.07	1.10 ± 0.10
Smoking (n - %) [c]	82–58.5%	73–52.1%
Glycemia (mmol/L 95% CI)	5.34–5.50	5.56–5.71 *
Glycated Haemoglobin (mmol/L 95% CI)	5.34–5.49	5.54–5.86 *
[a] Mean diabetes duration (± SD) was 9.71 (± 5.58) years		
[b] Half of each gender and group were between 50 and 59 years and the other half between 60 and 70 years old		
[c] All males except for 2 females in the diabetic group		
* $p < 0.01$		

[Table 1]

Participants were evenly assigned and paired as per health status (healthy/diabetic groups) and gender (male/female). Participants in each health status group were well balanced by menopausal status (females), mean age, BMI, hip to waist ratio, and smoking status.

The mean diabetes duration was 9.71 years in the T2D group. As expected, the 95% confidence interval (95% CI) of glycemia and glycated haemoglobin was significantly higher in the diabetic group than in the healthy group ($p < 0.01$).

3.2 The effect of T2D and age on skin complexion in the Chinese population

The statistical analysis of least square means of skin complexion variables between healthy and diabetic groups showed that skin complexion was mostly not associated to T2D (Table 2). Statistically significant difference was reported in dark circle around eyes being worse in the healthy group ($p < 0.05$) than T2D

group (Table 2). Other parameters as facial wrinkles severity, dyspigmentation, slackening, and bag under eyes were not significantly associated with health status (Table 2). Skin complexion was highly associated with gender. Skin phototype (3.83 vs 3.61 $p < 0.01$), skin type (3.31 vs 3.14 $p < 0.05$) and facial wrinkles severity (4.68 vs 4.45 $p < 0.01$) were higher in males than females. Males presented darker tan score and more dyspigmentation then females ($p < 0.01$). Cutaneous dryness (0.27 vs 0.20 $p < 0.05$) was higher in females. Females presented more cutaneous allergy and skin reaction to cosmetic products than males ($p < 0.01$).

Table 2
Least square means of grading of listed skin characteristics in healthy and diabetic groups

	HEALTHY	TYPE-2 DIABETES	p[a]
Facial Wrinkles Severity	4.53	**4.60**	ns
Dyspigmentation	**3.84**	3.82	ns
Skin Slackening	7.33	**7.43**	ns
Dark Circle around Eyes	**2.34**	2.25	< 0.05
Bag under Eyes	3.18	**3.21**	ns
GRADING: Facial Wrinkles Severity: grades 0–7, where 0 represent no wrinkles and 7 indicates severely wrinkled; Pigmentation: 6-point scale, with 0 representing no dyspigmentation and 5 representing severe dyspigmentation; Skin slackening *(Tsukuhara´s grading)*: 1–2 for slight, 3–4 for mild, 5–6 for moderate, 7–8 for severe, and 9–10 for very severe sagging; Dark circles around eyes *and* bags under eyes: scored with 1 for never, 2 for seldom, 3 for often, and 4 for always.			
[a] among the 4 healthy and T2D groups			

[Table 2]

The analysis of these same parameters, facial wrinkles severity, dyspigmentation, slackening, and bag under eyes by age group showed that the skin complexion worsens with age. The only difference was that the dark circle around the eyes were significantly different between age groups but not directly related to ageing (Table 3).

Table 3
Least square means of listed skin characteristics by age subgroups between healthy and T2D groups

AGE SUBGROUP *(age in years)*	**50–54**	**55–59**	**60–64**	**65–70**	**p** [a]
Facial Wrinkles Severity	3.93	4.43	4.62	**5.28**	< 0.01
Dyspigmentation	3.50	3.72	3.78	**4.32**	< 0.01
Skin Slackening	6.39	7.15	7.56	**8.43**	< 0.01
Dark Circle around Eyes	2.31	2.24	**2.44**	2.18	< 0.01
Bag under Eyes	2.99	3.13	3.17	**3.48**	< 0.01

GRADING: Facial Wrinkles Severity: grades 0–7, where 0 represent no wrinkles and 7 indicates severely wrinkled; Pigmentation: 6-point scale, with 0 representing no dyspigmentation and 5 representing severe dyspigmentation; Skin slackening *(Tsukuhara´s grading)*: 1–2 for slight, 3–4 for mild, 5–6 for moderate, 7–8 for severe, and 9–10 for very severe sagging; Dark circles around eyes *and* bags under eyes: scored with 1 for never, 2 for seldom, 3 for often, and 4 for always.

[a] among the 4 age groups

[Table 3]

3.3 Association of AGEs with health status, gender, and age

Our results showed that the least square mean of SAF was significantly higher ($p < 0.01$) in the T2D group (2.77) than in healthy group (2.56) and significantly higher ($p < 0.01$) in males (2.80) compared to females (2.54). In addition to diabetes and gender, age was also found to be directly related to SAF (Table 4). These results show a direct association with T2D and AGEs.

Table 4
Least square means of skin autofluorescence by health status, gender, and age subgroups

	Skin autofluorescence LSM				P [a]
Health Status	**Healthy**		**Type-2 diabetes**		< 0.01
	2.56		**2.77**		
Gender	**Males**		**Females**		< 0.01
	2.80		2.54		
Age subgroup	**50–54**	**55–59**	**60–64**	**65–70**	< 0.01
(age in years)	2.52	2.66	2.71	**2.78**	

[a] among all the respective groups

LSM: Least Square Means

[Table 4]

The correlation between the SAF and skin complexion (wrinkles and dyspigmentation) between the groups was further investigated. According to the 8-point scale method for measuring the severity of the wrinkles, most subjects were between grade 3–7, with only 1 subject grade 2 and no subjects in grades 0 and 1.

The mean ± SD and 95% CI of SAF were 2.52 ± 0.48, 95% CI: 2.39–2.64 for grade 3; 2.69 ± 0.59, 95% CI: 2.62–2.77 for grade 4; 2.68 ± 0.58, 95% CI: 2.59–2.76 for grade 5; 2.69 ± 0.55; 95% CI: 2.55–2.83 for grade 6 and 3.00 ± 1.04, 95% CI: 2.53–3.47 for grade 7 respectively. Due to the low number of subjects with grade 2 (n = 1) and grade 7 (n = 19), grade 2 was combined with grade 3, and grade 7 was combined with grade 6. (Fig. 1).

[FIGURE 1]

For dyspigmentation analysis, SAF results were 2.38 ± 0.56 (mean ± SD), 95% CI: 1.89–2.87 for grade 2; 2.57 ± 0.57, 95% CI: 2.49–2.65 for grade 3; 2.70 ± 0.59, 95% CI: 2.62–2.77 for grade 4; 2.81 ± 0.55, 95% CI: 2.69–2.92 for grade 5 and 3.19 ± 0.95, 95% CI: 2.67–3.71 for grade 6.

High standard deviation of SAF was observed in the group with grade 2 dyspigmentation, which might be due to the low number of volunteers (n = 5) in this group. Therefore, grade 2 (n = 5) was combined with grade 3, and the grade 6 (n = 13) was combined with grade 5.

The correlation was analysed among groups with combined grade 2 + 3, grade 4, and combined grade 5 + 6 (Fig. 2). ANOVA analysis showed that a significant correlation between the grade of dyspigmentation and SAF ($p < 0.01$).

[FIGURE 2]

3.4 Quality of Life Assessment

Healthy group had consistently higher significant values in most of the items of assessed.

The overall score for Quality of Life (Table 5) was significantly higher ($p < 0.01$) in healthy group (53.57 vs 55.38) as the three domains assessed (physical form, spirit, and emotion).

Table 5
Chinese Quality of Life Questionnaire scores

		HEALTHY	TYPE-2 DIABETES	p[a]
Physical Form	Complexion	**55.26**	53.22	< 0.05
	Sleep	**57.46**	54.99	< 0.05
	Stamina	**54.74**	53.29	< 0.05
	Appetite and Digestion	**55.66**	54.77	ns
	Adaptation to climate	**54.06**	52.65	ns
Spirit	Consciousness	**64.12**	60.61	< 0.01
	Thinking	**58.40**	55.62	< 0.01
	Spirit of Eye	**52.02**	51.24	ns
	Verbal Expression	**52.33**	51.02	< 0.05
Emotion	Joy	**55.11**	53.41	< 0.05
	Anger	**54.36**	52.50	< 0.01
	Depressed mood	**53.53**	51.82	< 0.01
	Fear & anxiety	**52.03**	50.77	ns
Domains	Physical form	**55.33**	53.73	< 0.01
	Spirit	**57.75**	55.37	< 0.01
	Emotion	**53.86**	52.19	< 0.01
Overall Quality of Life		**55.38**	**53.57**	**< 0.01**

[a] among all the respective groups

[Table 5]

4. Discussion

Previous studies have shown that epidermal barrier function and skin thickness are altered in diabetic patients and are correlated with glycaemic control and AGEs [25]. Skin elasticity is lost as years go by and the accumulation of AGEs in elderly people may contribute to this process [16].

The mean duration of diabetes among the subjects in the diabetic group was close to 10 years. During the study, the level of glycemia (95% CI: 5.56–5.71 mmol/L) of the diabetic group, although significantly higher than that of the healthy group, was less than the diagnostic standard of 7.0 mmol/L indicating a good glycaemic control in the diabetic group.

The overall score for Quality of Life was significantly higher ($p < 0.01$) in healthy group (53.57 vs 55.38) as the three domains assessed (physical form, spirit, and emotion).

Although normal dermatological changes occur with ageing, pathophysiological changes in the skin are more frequent in diabetic patients [27]. Elevated serum glucose levels and its pathophysiological components have been identified as responsible for this dermatological condition. The study showed that there is a lack of any clear influence of T2D when pharmacologically treated, in facial wrinkles severity, dyspigmentation, slackening, and bag under eyes which were in fact directly related to ageing when compared to this variable. The only investigated skin complexion parameter showing significant differences between the healthy and diabetic groups was dark circle around eyes that was documented to be worse in the healthy group ($p < 0.05$) than in the T2D group.

SAF level quantifies the glycation level on each individual and allows to study the possible correlations between the clinical signs of ageing and the glycation level. Some variation of SAF level was observed between the healthy and the diabetes group .

Dark circles around eyes parameter were not consistently influenced by ageing. Even if the differences dark circles around eyes in each age group were statistically significant, variations worsened and improved randomly with advancing age.

Other important parameters are AGEs with published evidence of their important role in skin ageing [28]. SAF has been used as an independent predictor of micro and macrovascular complications in studies previously conducted in Europe [11, 13]. This study confirmed that in the Chinese population across 4 sites, SAF was elevated in the diabetic group compared to the healthy group. We agree with the study results of Lutgers et al, where SAF was reported to be higher in T2D patients compared with age-matched control subjects [11]. Moreover, in the study SAF had a positive association with age which is conceivably related to increased glycation involved in the normal physiology of ageing skin [11].

Gender and ethnic factors may have an influence on SAF. However, their impact has not been as consistently determined as that of ageing [29, 30]. In this study SAF was reported higher in men than in women (Table 4). On the contrary, Koetsier et al. found a small, non-significant gender difference in certain sub-populations within current smokers with women having a higher SAF [12]. Furthermore, the

mean value of SAF for the healthy group in our study was 2.56, that in comparison to the results published by Yue et al. had better outcomes in the reference values given for the Chinese population [30].

When investigating the relationship between SAF and the wrinkle score and the dyspigmentation score, a correlation was observed between the SAF level and the dyspigmentation level. AGEs were shown to stimulate melanin synthesis and pigmentation *in vitro* by Lee [31] and could worsen skin dyspigmentation.

5. Conclusions

As observed from the data collected, this study with its current design could not identify any critical effects of diabetes on facial skin complexion parameters in the Chinese population. Parameters measured included facial wrinkles severity, dyspigmentation, slackening, and bag under eyes were found to be directly correlated with age, as expected, and hence adding control credibility to the data collected in this study.

Taken together, a multicentre study with 280 T2D and 280 healthy control subjects in China, confirmed that the SAF continues to be a reliable tool of AGEs accumulation which is related to long-term complications of diabetes [33], particularly in the cardiovascular field [34]. AGEs have also been related as biomarkers for different complications in T2D patients [35], different than the skin ones intended in this study. It also supported the fact that SAF shows differences in males than females and that gender, ethnicity and race may play a major role in these variations. Finally, these implications need to be substantiated with further research findings that explore more closely the biological links between glycation and pigmentation heterogeneity.

SAF was previously reported to be correlated with the skin yellowness linked to ageing, however no investigation on dyspigmentation was performed in that study [36]. Our study, for the first time, demonstrated a significant association between skin AF and dyspigmentation. The involvement of oxidative damage should be further investigated.

Abbreviations

AGEs: advanced glycation end products

SAF: skin autofluorescence

T2D: Type-2 diabetes

95% CI: 95% confidence interval

LSM: Least Square Means

Declarations

Ethics approval and consent to participate

An informed consent form was written in Chinese (native language) and signed by each participant.

The study was submitted and approved by the local ethics committee: Medical Research Ethics Committee, School of Public Health, Fudan University (IRB00002408 & FWA00002399)

Availability of data and materials

The datasets used and/or analysed during the current study are available from the corresponding author on reasonable request.

Competing interests

The authors have no conflicts of interest to declare.

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Authors' contributions

Tianxiang Ou-Yang is the main author; Jiayi Ni made the main statistical analysis, Delphine de Quéral applied the study questionnaire and in the statistical analysis, Catherine Heusèle is the corresponding author, Sylvianne Schnebert contributed to the analysis of the results.

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References

1. Alberti KG, Zimmet, PZ. Definition, Diagnosis, and Classification of Diabetes Mellitus and its Complications. Part 1: Diagnosis and Classification of Diabetes Mellitus. Provisional report of WHO consultation. 1998;15(7):539–53. https://doi.org/10.1002/(sici)1096-9136(199807)15:7%3C539::aid-dia668%3E3.0.co;2-s
2. Ahmed I, Goldstein B. Diabetes mellitus. Clin Dermatol. 2006; 24:237–246. https://doi.org/10.1016/j.clindermatol.2006.04.009
3. Behm B, Schreml S, Landthaler M, et al. (2012) Skin signs in diabetes mellitus. *J Eur Acad Dermatol Venereol*. 2012;26(10):1203–1211. https://doi.org/10.1111/j.1468-3083.2012.04475.x
4. Noordam R, Gunn Da, Tomlin CC, et al. High serum glucose levels are associated with a higher perceived age. Age. 2011; 35:189–195. https://doi.org/10.1007/s11357-011-9339-9

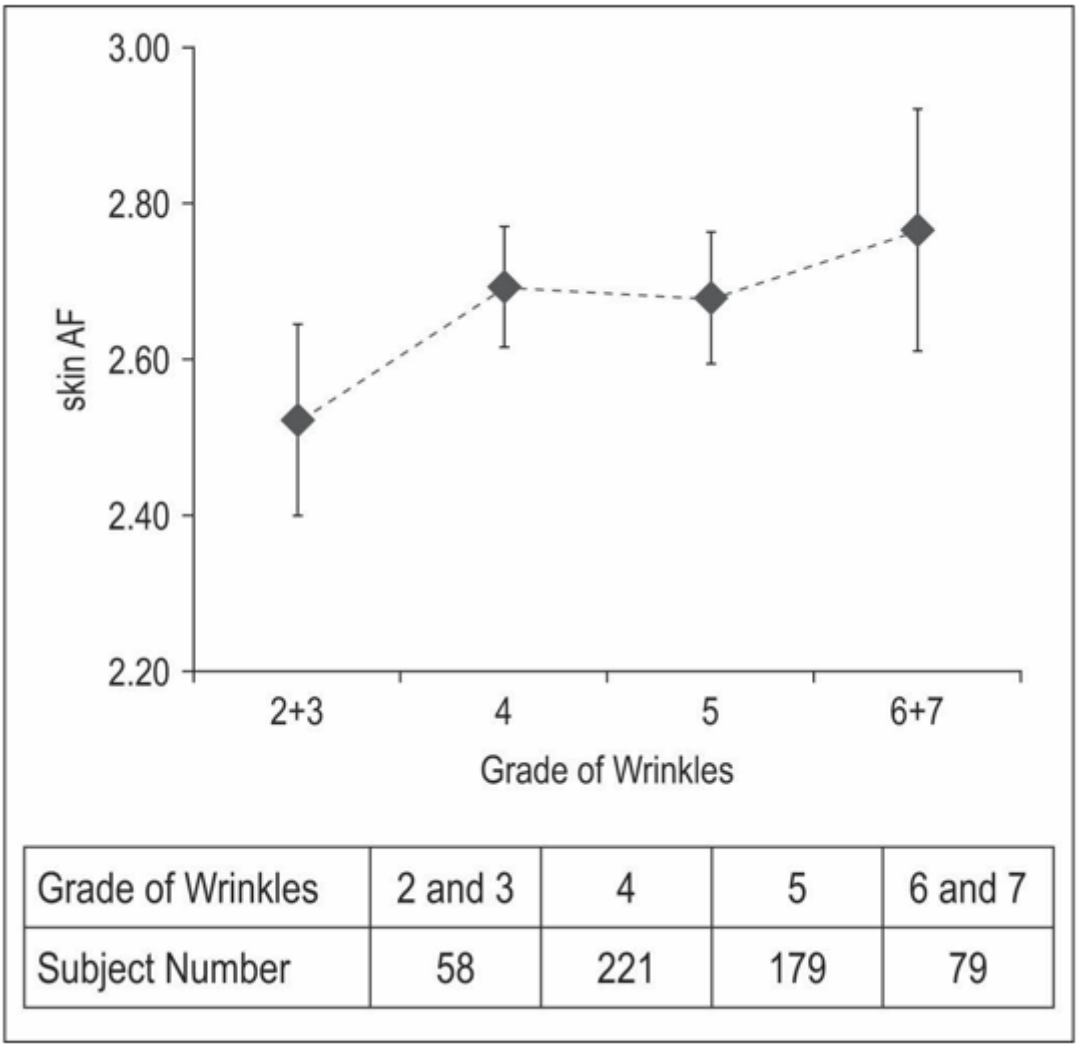
5. Singh R, Barden A, Mori T, Beilin L. Advanced glycation end-products: a review. Diabetologia 2001;44(2):129–46. https://doi.org/10.1007/s001250051591
6. Sachdeva S. Fitzpatrick skin typing: Applications in dermatology. Indian J Dermatol Venereol Leprol. 2009;75(1):93–6. https://doi.org/10.4103/0378-6323.45238
7. Sharma C., Kaur A., Thind SS., et al. Advanced glycation End-products (AGEs): an emerging concern for processed food industries. J Food Sci Technol. 2015;52(12):7561–76. https://dx.doi.org/10.1007%2Fs13197-015-1851-y
8. Wells-Knecht KJ, Brinkmann E, Wells-Knecht MC, et al. New biomarkers of Maillard reaction damage to proteins. *Nephrol Dial Transplant*. 1196;11 Suppl 5:41 – 7. https://doi.org/10.1093/ndt/11.supp5.41
9. Jeanmaire C, Danoux L, Pauly G. Glycation during human dermal intrinsic and actinic aging: an in vivo and in vitro model study. Br J Dermatol Suppl. 2001;145(1):10–18 https://doi.org/10.1046/j.1365-2133.2001.04275.x
10. Ahmed N. Advanced glycation endproducts–role in pathology of diabetic complications. Diab Res. 2005;67(1):3–21. https://doi.org/10.1016/j.diabres.2004.09.004
11. Gerrits EG, Lutgers HL, Kleefstra N, et al. Skin autofluorescence: a tool to identify type 2 diabetic patients at risk for developing microvascular complications. Diabetes care. 2008;31(3):517–21. https://doi.org/10.2337/dc07-1755
12. Koetsier M, Lutgers HL, de Jonge C, et al. Reference values of skin autofluorescence. Diabetes Technol Ther. 2010;12(5):399–403. https://doi.org/10.1089/dia.2009.0113
13. Lutgers HL, Graaff R, Links TP, et al. Skin Autofluorescence as a Noninvasive Marker of Vascular Damage in Patients with Type 2 Diabetes. Diabetes Care. 2006;29(12):2654–9. https://doi.org/10.2337/dc05-2173
14. Meerwaldt R, Graaff R, Oomen PHN, et al. Simple non-invasive assessment of advanced glycation endproduct accumulation. Diabetologia. 2004; 47:1324–30. https://doi.org/10.1007/s00125-004-1451-2
15. Monami M, Lamanna C, Gori F, et al. Skin autofluorescence in type 2 diabetes: Beyond blood glucose. Diab Res Clin Pract. 2008;79(1):56–60. https://doi.org/10.1016/j.diabres.2007.07.007
16. 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(7):663–67. https://doi.org/10.1016/j.exger.2008.01.012
17. Weiwei He, Qiushi Xu, Lili Han, et al. Using real-world data to estimate the changing trends in the prevalence and incidence of type 2 diabetes mellitus in Xiamen of China from 2014 to 2019. BMC Endocr Disord. 2021; 21: 92. https://dx.doi.org/10.1186%2Fs12902-021-00759-w
18. J. Weng, L. Ji, W. Jia et al. Standards of care for type 2 diabetes in China. Diab Metab Res Rev.2016;32(5):442–48. https://doi.org/10.1002/dmrr.3158
19. Zhang XX, Kong J, Yun K. Prevalence of Diabetic Nephropathy among Patients with Type 2 Diabetes Mellitus in China: A Meta-Analysis of Observational Studies. J. Diabetes Res. 2020; 2315607:11.

https://doi.org/10.1155/2020/2315607

20. American Diabetes Association. Classification and Diagnosis of Diabetes: Standards of Medical Care in Diabetes 2021. Diab Care 2021;44(1): S15–S33. https://doi.org/10.2337/dc21-S002
21. Leung K, Liu F, Zhao L, et al. Development and validation of the Chinese Quality of Life Instrument. Health Qual Life Out. 2005;(3):26. https://doi.org/10.1186/1477-7525-3-26
22. Chung JH, Lee SH, Youn CS, et al. Cutaneous photodamage in Koreans: influence of sex, sun exposure, smoking, and skin color. Arch Dermatol. 2001;137(8):1043–51 PMID: 11493097
23. Tsukahara K, Takema Y, Fujimura T, et al. Determination of age-related changes in the morphological structure (sagging) of the human cheek using a photonumeric scale and three-dimensional surface parameters. Int J Cosmet Sci. 2000;22(4):247–58. https://doi.org/10.1046/j.1467-2494.2000.00033.x
24. Sachdeva S. Fitzpatrick skin typing: Applications in dermatology. Indian J Dermatol Venereol Leprol. 2009;75(1):93–6. https://doi.org/10.4103/0378-6323.45238
25. De Macedo G.M.C., Nunes S., Barreto T. Skin disorders in diabetes mellitus: an epidemiology and physiopathology review. Diabetol Metab Syndr. 2016;8,63. https://doi.org/10.1186/s13098-016-0176-y
26. Tailleux A., Duriez P, Fruchart JC, et al. Apolipoprotein A-II, HDL metabolism and atherosclerosis. Atherosclerosis. 2002;164(1):1–13. https://doi.org/10.1016/s0021-9150(01)00751-1
27. Rosen J, Yosipovitch G. Skin Manifestations of Diabetes Mellitus. [Updated 2018 Jan 4]. In: Feingold KR, Anawalt B, Boyce A, et al., editors. *Endotext* [Internet]. South Dartmouth (MA): MDText.com, Inc.; 2000-. Available from: https://www.ncbi.nlm.nih.gov/books/NBK481900/
28. Gkogkolou, P., & Böhm, M. Advanced glycation end products: Key players in skin aging? Dermatoendocrinol. 2012;4(3), 259–70. https://doi.org/10.4161/derm.22028
29. Mook-Kanamori M. J., Selim M. M., Takiddin A. H., et al. Ethnic and gender differences in advanced glycation end products measured by skin auto-fluorescence. Dermatoendocrinol, 2013;5(2):325–30. https://doi.org/10.4161/derm.26046
30. Morvova M., Jr., Jeczko P., Sikurova L. Gender differences in the fluorescence of human skin in young healthy adults. Skin Res. Technol. 2018; 24:599–605. https://doi.org/10.1111/srt.12471
31. Lee, E., Kim, J. & Oh, S. Advanced glycation end products (AGEs) promote melanogenesis through receptor for AGEs. Sci Rep. 2016;6 :27848. https://doi.org/10.1038/srep27848
32. Yue X, Hu H, Koetsier M, et al. Reference values for the Chinese population of skin autofluorescence as a marker of advanced glycation end products accumulated in tissue. Diabet Med. 2011;28(7):818–23. https://doi.org/10.1111/j.1464-5491.2010.03217.x
33. Fokkens, B. T., & Smit, A. J. Skin fluorescence as a clinical tool for non-invasive assessment of advanced glycation and long-term complications of diabetes. Glycoconj J. 2016;33(4):527–35. https://doi.org/10.1007/s10719-016-9683-1

34. Blanc-Bisson C., Velayoudom-Cephise F. L., Cougnard-Gregoire A., et al. Skin autofluorescence predicts major adverse cardiovascular events in patients with type 1 diabetes: a 7-year follow-up study. Cardiovasc Diabetol. 2018;17(1):82. https://doi.org/10.1186/s12933-018-0718-8
35. Hosseini, M. S., Razavi, Z., Ehsani, A. H., et al. Clinical Significance of Non-invasive Skin Autofluorescence Measurement in Patients with Diabetes: A Systematic Review and Meta-analysis. Eclinical Medicine. 2021;42:101194. https://doi.org/10.1016/j.eclinm.2021.101194
36. Ohshima H, Oyobikawa M, Tada A, et al. Melanin and facial skin fluorescence as markers of yellowish discoloration with aging. Skin Res Tech. 2009; 15(4):496–502. https://doi.org/10.1111/j.1600-0846.2009.00396.x

Figures

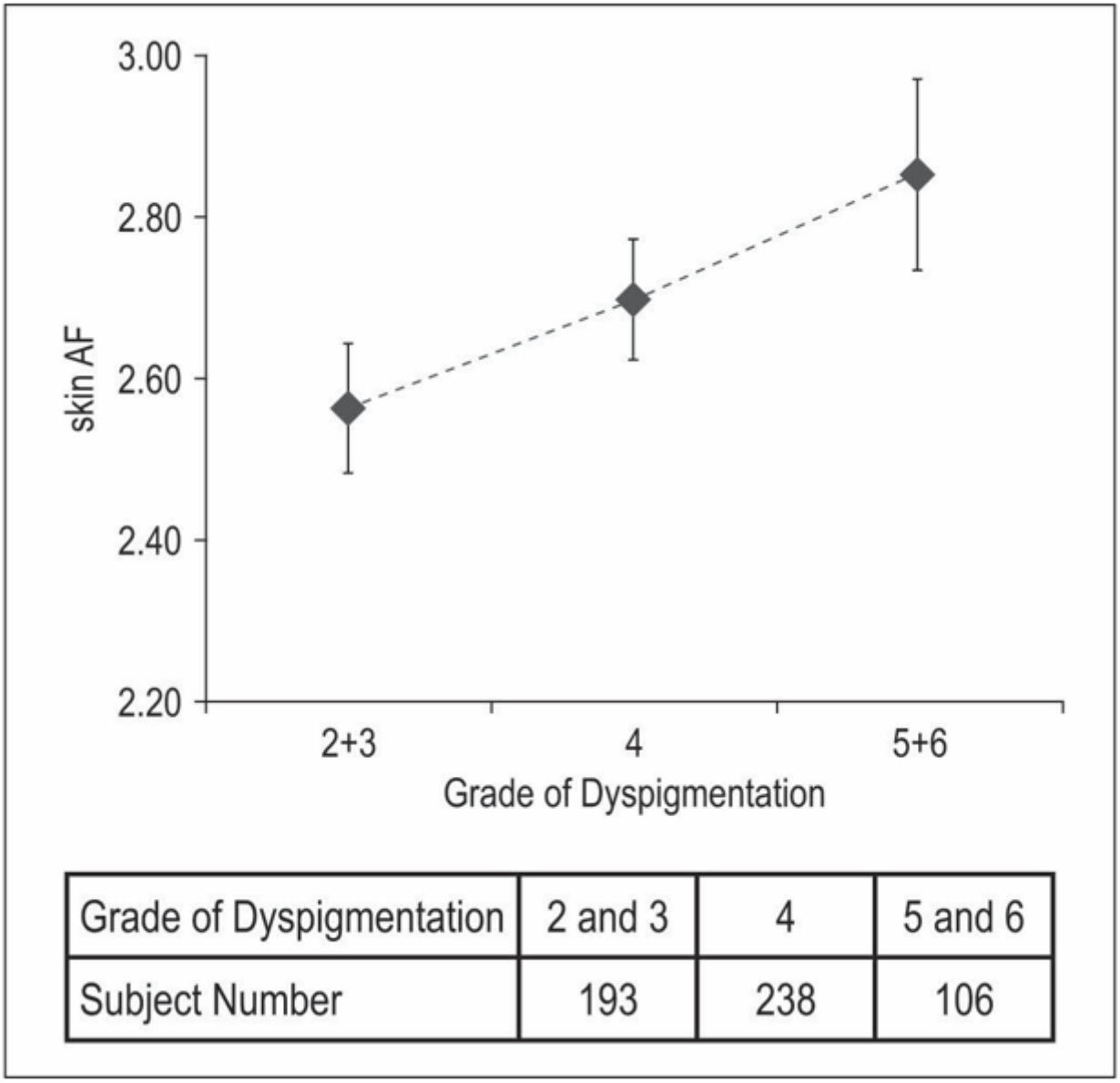


Grade of Wrinkles	2 and 3	4	5	6 and 7
Subject Number	58	221	179	79

Figure 1

No significant association between the severity of face wrinkles assessed by a

dermatologist with SAF.



Grade of Dyspigmentation	2 and 3	4	5 and 6
Subject Number	193	238	106

Figure 2

Correlation between the severity of face dyspigmentation assessed by a dermatologist with SAF ($p<0.01$)