Advanced Glycation End Products, a Potential Link between Psoriasis and Cardiovascular Disease: A Case-control Study

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Abstract

Context: Advanced glycation end products (AGEs) promote oxidative stress and inflammation by altering structure and function of proteins. They are excessively produced mainly in hyperglycemia, chronic inflammation and are involved in the development of atherosclerosis and cardiovascular disease. Aims: The aim of this study was to investigate whether skin AGEs levels were increased and had relation to premature atherosclerosis in patients with psoriasis. Subjects and Methods: Fifty-two psoriasis patients and 20 healthy controls (HC) were included. AGEs were determined by skin autofluorescence (SAF) analysis. High-sensitive C-reactive protein (hsCRP) and carotid intima-media thickness (CIMT) were also investigated. Physical activity and dietary patterns were determined. Statistical Analysis Used: Fisher’s exact test, two-sample t-tests, Mann–Whitney-U test, Pearson correlation, Spearman correlation, and Wilcoxon test. Results: SAFs were increased in psoriasis patients (1.8 arbitrary units [AUs]) compared to that in HC (1.6 AUs) (P = 0.057). Median CIMT values of HC and psoriasis groups were 0.43 (0.28–0.79), and 0.59 (0.44–0.98) respectively and the differences were significant (P = 0.001); hsCRP levels were not different between groups. Conclusions: Skin AGE accumulation was found to have a correlation with CIMT in psoriasis patients providing evidence for the role of AGEs in premature atherosclerosis.

Key Words: Advanced glycation end-products, atherosclerosis, cardiovascular morbidity, carotid intima-media thickness, psoriasis

Introduction

Psoriasis is a chronic, immune-mediated inflammatory disease with an increased risk of cardiovascular morbidity which has been evidenced by various studies and two recent systematic reviews.[5-9] Chronic psoriatic inflammation has been linked to cardiovascular morbidity as current data support relation to disease severity, persistence even after adjustment of traditional cardiovascular risk factors and beneficial effects of anti-inflammatory treatments including TNF-α inhibitors and methotrexate on cardiovascular outcomes.[6-9] Although inflammatory cytokines such as IL-6, IL-1, and TNF-α are proposed to have a role, data on pathogenetic pathways and molecules are limited.[3]

Advanced glycation end products (AGEs) are the products of nonenzymatic glycation and oxidation of proteins and lipids which alter their structure and function. They are endogenously formed in small amounts under physiological conditions but hyperglycemia, inflammation, hypoxia, and oxidative stress may increase formation of AGEs. They are also taken exogenously with diet, modern western diet being a rich source of them. Among various effects, AGEs mediate pro-atherogenic and proinflammatory effects through increased reactive oxygen species (ROS) production and subsequent nuclear factor-kappa B (NF-kB) activation. This leads to transcription of proinflammatory cytokines IL-6 and TNF-α genes, which are known to promote endothelial dysfunction [Figure 1]. As such, AGEs have been shown to have significant role in the pathogenesis of diabetic nephropathy, atherosclerosis, and cardiovascular diseases of diabetic adults and children.[8-10]

We hypothesize accumulation of AGEs by chronic inflammatory state to be a potential mechanism for...
atherogenesis in patients with psoriasis. To test this hypothesis, we aimed to investigate skin AGEs levels in psoriasis patients and to find out their relation to carotid intima-media thickness (CIMT) and high-sensitive C-reactive protein (hsCRP) as surrogate markers of atherosclerosis. We also aimed to investigate:

- The relation of CIMT with physical activity
- Change of AGEs and CIMT following 3 months of methotrexate treatment
- Correlation between CIMT, AGEs, and hsCRP.

**Subjects and Methods**

**Subjects**

This was a case–control study that included 52 moderate-to-severe plaque psoriasis determined by PASI >10, BSA >10, and 20 healthy controls. Exclusion criteria were as follows:

- The presence of diabetes according to criteria defined by the American Diabetes Association\(^{[11]}\)
- Chronic renal or liver disease, malignancy, hypertension, or hyperlipidemia
- Having myocardial infarction, stroke, severe infection, or sepsis within the last 3 months
- Any systemic treatment including phototherapy or disease modifying medications within the last 3 months
- Sunburn or tanning which may cause false elevation of skin AGEs.

All subjects had body mass index calculation and hsCRP assessment in addition to metabolic profile. The study was approved by the Local Ethics Committee and a written informed consent was obtained from each study participant.

**Advanced glycation end products and other measurements**

Skin AGEs measurements were performed by the noninvasive autofluorescence technique. The device was held 10 cm away from healthy right and left forearm skin and spectrometric evaluation of a 4 cm² sized area was performed (AGE-Reader DiagnOptics BV Groningen, The Netherlands). All measurements were performed by a single, experienced analyst. SAF values were expressed in arbitrary units (AU) calculated through dividing the average light intensity emitted by skin (per nm over the range from 420 nm to 600 nm) by the average excitation light intensity emitted from internal light source of the device (per nm over the range from 300 nm to 420 nm), and the quotient was multiplied by 100.

**Measurement of carotid intima-media thickness**

A single experienced vascular sonographer blinded to clinical data performed imaging. CIMT was measured by using a standard 10 MHz linear array transducer and GE Vingmed, System Five (Horten, Norway). The patient was in supine position with the head turned approximately 45° in the opposite direction of the ultrasonographer. The CIMT measurements were obtained from the distal 2 cm of the common carotid artery, proximal to its bifurcation. The longitudinal B-mode image was accepted as valid when a double parallel line resembling lumen-intima and media-adventitia interfaces was visualized. The distance between these two interfaces indicated the CIMT. At end-diastole CIMT of the far walls of the right and left common carotid arteries were measured manually at three points, using the leading edge convention, and the mean value was calculated.\(^{[12]}\)

**Assessment of leisure time physical activity**

Since AGE levels can be affected by physical exercise and both American and European guidelines recommend physical activity as a key element for cardiovascular protection, physical activity was assessed, through an interview.\(^{[13-16]}\)

Accordingly following categories and a score ranging from 1 to 3 were defined

1. Sedentary
2. ≥30 min of moderate-intensity aerobic exercise ≥5 days/week
3. ≥25 min of vigorous aerobic exercise ≥3 days/week and moderate-to-high intensity muscle strengthening activity ≥2 days/week.

**Treatment**

Because the efficacy studies of methotrexate in psoriasis usually target PASI-75 response in 12 weeks, hsCRP, AGEs, and CIMT measurements were repeated in 11 psoriasis patients following 12 weeks of methotrexate treatment (15 mg/week).

**Statistical methods**

Categorical variables were analyzed by the Fisher’s exact test. Two-sample *t*-test or Mann–Whitney U-test was used to compare patients and controls for continuous variables. Gaussian distribution of the data was analyzed with the Pearson omnibus normality test. The correlation analysis was performed by Pearson correlation when variables were distributed normally; otherwise, the Spearman correlation was used. Wilcoxon test was used to compare continuous variables between paired groups. Differences with *P* < 0.05 were considered statistically significant.

Analyses were performed using SPSS version 14.0 (SPSS Inc., Chicago, Illinois, USA).

**Results**

**Demographic features and cardiovascular risk factors**

Fifty-two psoriasis patients (PASI >10) and 20 healthy controls aged 21–58 and 25–48 years respectively were
included. Demographic data are shown in Table 1. Although psoriasis patients had higher BMI than healthy individuals, the difference was insignificant \( (P = 0.071) \).

**Carotid intima-media thickness**

Median CIMT values of healthy and psoriasis groups were 0.43 mm (0.28–0.79) and 0.59 (0.44–0.98), respectively. The difference between these values was statistically significant \( (P < 0.01) \).

A positive correlation was found between CIMT and AGEs levels \( (r = 0.302, P = 0.049) \) [Table 2].

**Advanced glycation end products and other measurements**

Baseline median AGEs levels of healthy and psoriasis groups were 1.60 (0.11–2.30) and 1.80 (1.2–2.7) AU, respectively. When groups were compared, albeit statistically insignificant psoriasis group had higher median AGEs levels \( (P = 0.057) \). AGEs levels had statistically significant positive correlation with BMI \( (r = 0.416, P = 0.007) \).

Baseline median hsCRP values of healthy and psoriasis groups were 1.03 (0–4.37) and 0.43 (0–9.58) mg/L, respectively, with no statistically significant difference \( (P = 0.14) \). The hsCRP had a moderate correlation with BMI. Psoriasis patients having higher BMI also had higher hsCRP levels [Table 2].

**Leisure time physical activity**

Of the psoriasis patients 46.9% and of the healthy controls 60% individuals scored 2 or 3 from leisure time physical activity evaluation indicating sufficient or good activity. However, the difference was not statistically significant \( (P = 0.325) \).

**Treatment**

Among psoriasis patients, 11 were treated with methotrexate. These were re-evaluated after 3 months of treatment, for hsCRP, AGEs, and CIMT. Baseline and after treatment measurements were analyzed. Although median AGEs level decreased from 1.80 to 1.60, this change was insignificant \( (P = 0.216) \). Likewise, no significant change could be obtained in CIMT values after treatment \( (P = 0.636) \).

**Discussion**

Since the role of AGEs in human atherosclerosis has been supported by ample evidence, we have investigated their levels and relation to CIMT in patients with psoriasis, a chronic inflammatory disease being an independent risk factor for the development of cardiovascular disease.\(^{[17]}\) We have found higher CIMT levels in patients with psoriasis compared to controls. However, levels of skin autofluorescent AGEs, albeit being higher in psoriasis group, were not significantly different from healthy group.

| Characteristics          | Healthy \((n=20)\) | Psoriasis \((n=52)\) | \(P\) |
|--------------------------|------------------|-------------------|-----|
| Age (median)             | 32 (25-48)       | 36 (21-58)        | 0.142 |
| (minimum-maximum)        |                  |                   |     |
| Sex, n (%)               |                  |                   |     |
| Female                   | 16 (80)          | 29 (55.8)         | 0.057 |
| Male                     | 4 (20)           | 23 (44.2)         |     |
| BMI (mean±SD)            | 24.27±3.18       | 26.75±5.24        | 0.071 |
| hsCRP (median)           | 1.03 (0-4.3)     | 0.43 (0-9.58)     | 0.140 |
| (minimum-maximum)        |                  |                   |     |

BMI: Body mass index, hsCRP: High-sensitive C-reactive protein, SD: Standard deviation

| Table 2: Spearman’s correlation coefficients between body mass index, advanced glycation end products, carotid intima-media thickness and high-sensitive C-reactive protein values in patients with psoriasis |
|-------------------------------------------------|------------------|------------------|-----|
|                                        | \(\rho\) | \(P\) | \(\rho\) | \(P\) | \(\rho\) | \(P\) |
| BMI                                       | 0.535   | 0.000 | 0.210 | 0.088 | 0.416 | 0.007 |
| hsCRP                                    | -0.113  | 0.417 | 0.124 | 0.498 |
| CIMT-baseline                             | 0.302   | 0.049 |

BMI: Body mass index, AGEs: Advanced glycation end products, CIMT: Carotid intima-media thickness, hsCRP: High-sensitive C-reactive protein

The link of AGEs to atherosclerosis depends on various pathogenetic pathways. AGEs cause oxidative stress, endothelial inflammation, decrease elasticity of vessel wall due to modification of elastin structure, increase stiffness of blood vessels due to crosslinking on collagen, lead to accumulation of glycated LDL and decrease nitric oxide which is a vasodilator molecule counteracting atherosclerosis.\(^{[18,19]}\) In addition to atherosclerosis, they have been claimed to be involved in the pathogenesis of diabetic complications, fatty liver disease, natural aging, Alzheimer’s disease, rheumatoid arthritis, systemic lupus erythematosus, and Still’s disease.\(^{[20-22]}\) The binding of AGEs to their receptor has been shown to activate NF-κB which eventually leads to transcription of inflammatory genes.\(^{[23,24]}\) Furthermore, the inhibition of AGEs with aminoguanidine in mice has been shown to decrease serum levels of TNF-α and IL-6, providing further support to the link between inflammation mediated by AGEs.\(^{[25]}\) Recent data have revealed TNF-α to cause insulin resistance by enhancing adipocyte lipolysis and IL-6 through reducing the expression of glucose transporter 4 (GLUT4), insulin receptor substrate-1 (IRS-1), and also impairing the synthesis of glycogen.\(^{[26-28]}\) Although the causality cannot be proved, these data might implicate AGEs to cause insulin resistance, which was major underlying abnormality driving cardiovascular disease, through inducing the
release of TNF-α and IL-6. Albeit insignificant, AGEs in our patients with psoriasis were higher compared to controls. The literature on association between AGEs and psoriasis is sparse. A recent study showed increased AGE peptides in sera of 80 psoriasis patients compared to controls. The authors also reported a significant decrease in AGEs following remission obtained by different therapeutic methods without providing further information on modality, duration of treatment and response rate.[20] We also observed a decrease in AGEs levels following treatment which did not reach statistical significance, which might be related to small sample size or short treatment period. In another study addressing AGEs levels in psoriasis, Kaur et al. reported significantly higher serum methylglyoxal (an AGE precursor) levels in 60 psoriasis patients.[21] Another recent study by Papagrigoraki et al. also highlighted the possible role of AGEs in psoriasis. These authors have found increased skin and serum levels of AGEs in patients with severe psoriasis compared to controls and to those with mild disease. Furthermore, the authors also reported a strong correlation between skin and serum AGEs levels.[29] Although none of these studies attempted to address the relation between psoriasis and cardiovascular disease, these findings, in line with ours, indicate that there may be a link between inflammation and AGEs.

Even though patients with traditional risk factors for CVD such as diabetes, hyperlipidemia, and hypertension were excluded, and BMI and physical activity were indifferent from healthy group, we still found significantly higher CIMT values in our patients with psoriasis. CIMT is a measure of early atherosclerosis having a graded increase in cardiovascular risk with increasing CIMT.[22] Since our psoriasis group consisted of patients with moderate-to-severe disease, our findings provided further evidence on the role of chronic inflammation as being an additional risk factor for CVD in psoriasis patients. Indeed, a positive correlation between hsCRP and BMI in our psoriasis group further supported this view. Although methotrexate use in psoriasis and rheumatologic disorders had been shown to be associated with lower risk of CVD, we were unable to find any change in CIMT following methotrexate treatment.[36] This might be due to short treatment duration which failed to detect minor changes.

Regarding the lifestyle, 46.9% of our patients with psoriasis had sufficient physical activity which was slightly and insignificantly less than healthy group. Considering the fact that patients with psoriasis, besides disease per se, have higher risk of having traditional risk factors for CVD such as metabolic syndrome and smoking, patients should be trained and encouraged to comply with healthy lifestyle behaviors. The consequences of such training in routine management may be an interesting issue of research.

There are several limitations of our study. One was the use of skin autofluorescence which was unable to detect nonfluorescent AGEs. Thus, measurement of serum AGEs levels could have provided more precise data. However, skin autofluorescence, as a noninvasive measure, has been shown to correlate with serum AGEs, mean HbA1c levels, and diabetic long-term complications, indicating this method to be a valuable marker.[29,31-34] Another limitation of the present study was the small number of healthy controls, as well as the availability of the posttreatment data in only 11 patients, which decreased the statistical power of our results. Nevertheless, our study was the first in terms of providing data on AGEs and atherosclerosis and also on gathering information on physical activity patterns of psoriasis patients to evaluate the issue in holistic manner.

What are the practical consequences of our findings? If atherogenic role of AGEs is supported with new studies, strategies to restrict their levels can be considered in the management of psoriasis patients. Effective disease control to decrease inflammatory burden is one measure. Dietary AGEs restriction, as another strategy, can be achieved by increasing the consumption of fish, legumes, low-fat milk products, vegetables, fruits, whole grains, reducing intake of solid fats, fatty meats, full-fat dairy products, highly processed food, and also changing the cooking method from frying or broiling to steaming and brewing which have been shown to decrease serum AGEs by 30%–40%.[15-18] As preliminary data point out various medications including metformin, pentoxyfylline, and pyridoxamine to be promising anti-AGE agents, the efficacy of their use can also be investigated.[39] Thus, it may be interesting to find out whether long-term AGE restriction may provide beneficial outcome in the management of psoriasis, especially in terms of CVD prevention.

**Conclusions**

Our study points out that high AGEs may play a role to facilitate the emergence of CVD in psoriasis patients. The investigation of the consequences of AGEs restriction in CVD prevention in psoriasis patients may further illuminate the link between AGEs and cardiovascular comorbidity.

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**Conflicts of interest**

There are no conflicts of interest.
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