Indian Journal of Dermatology

ORIGINAL ARTICLE
Year : 2019 | **Volume** : 64 | **Issue** : 3 | **Page** : 201--206

Advanced glycation end products, a potential link between psoriasis and cardiovascular disease: A case–control study

Tulin Ergun[1], Vildan Yazici[2], Dilek Yavuz[3], Dilek Seckin-Gencosmanoglu[1], Gulsen Ozen[4], Andac Salman[1], Haner Direskeneli[4], Nevsun Inanc[4],

[1] Department of Dermatology, Marmara University School of Medicine, Istanbul, Turkey
[2] Department of Dermatology, Gebze Medical Park Hospital, Kocaeli, Turkey
[3] Department of Endocrinology, Marmara University School of Medicine, Istanbul, Turkey
[4] Department of Rheumatology, Marmara University School of Medicine, Istanbul, Turkey

Correspondence Address:
Dr. Andac Salman
Department of Dermatology Marmara University School of Medicine, Pendik Research and Training Hospital, Fevzi Cakmak Mah, Mimar Sinan Cad., No: 4134899, Pendik, Istanbul
Turkey

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.

How to cite this article:
Ergun T, Yazici V, Yavuz D, Seckin-Gencosmanoglu D, Ozen G, Salman A, Direskeneli H, Inanc N. Advanced glycation end products, a potential link between psoriasis and cardiovascular disease: A case–control study.Indian J Dermatol 2019;64:201-206

How to cite this URL:
Ergun T, Yazici V, Yavuz D, Seckin-Gencosmanoglu D, Ozen G, Salman A, Direskeneli H, Inanc N. Advanced glycation end products, a potential link between psoriasis and cardiovascular disease: A case–control study. Indian J Dermatol [serial online] 2019 [cited 2022 Mar 7];64:201-206
Available from: https://www.e-ijd.org/text.asp?2019/64/3/201/258623

Full Text

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.[1],[2],[3],[4],[5] 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.[2],[6],[7] 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-κB) 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],[9],[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 activityChange of AGEs and CIMT following 3 months of methotrexate treatmentCorrelation 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 hyperlipidemiaHaving myocardial infarction, stroke, severe infection, or sepsis within the last 3 monthsAny systemic treatment including phototherapy or disease modifying medications within the last 3 monthsSunburn 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],[14],[15],[16]

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

Sedentar≥30 min of moderate-intensity aerobic exercise ≥5 days/week≥25 min of vigorous aerobicexercise ≥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 ($P = 0.071$).{Table 1}

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].{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/lt, 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.

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],[21],[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],[27],[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 serum and skin 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.[30] 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],[32],[33],[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%.[35],[36],[37],[38] 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.

Acknowledgments

The authors would like to thank the Turkish Society of Dermatology for the funding of the study.

Financial support and sponsorship

This work was supported by the Turkish Society of Dermatology AG-23188 and AG-09453.

Conflicts of interest

There are no conflicts of interest.

References

1 Ahlehoff O, Gislason GH, Charlot M, Jørgensen CH, Lindhardsen J, Olesen JB, *et al.* Psoriasis is associated with clinically significant cardiovascular risk: A Danish Nationwide Cohort Study. J Intern Med 2011;270:147-57.

2 Gelfand JM, Neimann AL, Shin DB, Wang X, Margolis DJ, Troxel AB, *et al.* Risk of myocardial infarction in patients with psoriasis. JAMA 2006;296:1735-41.

3 Hugh J, Van Voorhees AS, Nijhawan RI, Bagel J, Lebwohl M, Blauvelt A, *et al.* From the medical board of the national psoriasis foundation: The risk of cardiovascular disease in individuals with psoriasis and the potential impact of current therapies. J Am Acad Dermatol 2014;70:168-77.

4 Armstrong EJ, Harskamp CT, Armstrong AW. Psoriasis and major adverse cardiovascular events: A systematic review and meta-analysis of observational studies. J Am Heart Assoc 2013;2:e000062.

5 Horreau C, Pouplard C, Brenaut E, Barnetche T, Misery L, Cribier B, *et al.* Cardiovascular morbidity and mortality in psoriasis and psoriatic arthritis: A systematic literature review. J Eur Acad Dermatol Venereol 2013;27 Suppl 3:12-29.

6 Roubille C, Richer V, Starnino T, McCourt C, McFarlane A, Fleming P, *et al.* The effects of tumour necrosis factor inhibitors, methotrexate, non-steroidal anti-inflammatory drugs and corticosteroids on cardiovascular events in rheumatoid arthritis, psoriasis and psoriatic arthritis: A systematic review and meta-analysis. Ann Rheum Dis 2015;74:480-9.

7 Armstrong AW, Brezinski EA, Follansbee MR, Armstrong EJ. Effects of biologic agents and other disease-modifying antirheumatic drugs on cardiovascular outcomes in psoriasis and psoriatic arthritis: A systematic review. Curr Pharm Des 2014;20:500-12.

8 Ueno H, Koyama H, Tanaka S, Fukumoto S, Shinohara K, Shoji T, *et al.* Skin autofluorescence, a marker for advanced glycation end product accumulation, is associated with arterial stiffness in patients with end-stage renal disease. Metabolism 2008;57:1452-7.

9 Chiarelli F, de Martino M, Mezzetti A, Catino M, Morgese G, Cuccurullo F, *et al.* Advanced glycation end products in children and adolescents with diabetes: Relation to glycemic control and early microvascular complications. J Pediatr 1999;134:486-91.

10 Rizvi AA. Cytokine biomarkers, endothelial inflammation, and atherosclerosis in the metabolic syndrome: Emerging concepts. Am J Med Sci 2009;338:310-8.

11 American Diabetes Association. (2) classification and diagnosis of diabetes. Diabetes Care 2015;38 Suppl 1:S8-16.

12 Fathi R, Marwick TH. Noninvasive tests of vascular function and structure: Why and how to perform them. Am Heart J 2001;141:694-703.

13 Momma H, Niu K, Kobayashi Y, Guan L, Sato M, Guo H, *et al.* Skin advanced glycation end product accumulation and muscle strength among adult men. Eur J Appl Physiol 2011;111:1545-52.

14 Yoshikawa T, Miyazaki A, Fujimoto S. Decrease in serum levels of advanced glycation end-products by short-term lifestyle modification in non-diabetic middle-aged females. Med Sci Monit 2009;15:PH65-73.

15 Authors/Task Force Members, Piepoli MF, Hoes AW, Agewall S, Albus C, Brotons C, *et al.* 2016 European Guidelines on Cardiovascular disease prevention in clinical practice: The sixth joint task force of the European Society of Cardiology and other Societies on Cardiovascular Disease Prevention in Clinical Practice (constituted by representatives of 10 societies and by invited experts): Developed with the special contribution of the European Association for Cardiovascular Prevention & Rehabilitation (EACPR). Eur J Prev Cardiol 2016;23:NP1-96.

16 Eckel RH, Jakicic JM, Ard JD, de Jesus JM, Houston Miller N, Hubbard VS, *et al.* 2013 AHA/ACC guideline on lifestyle management to reduce cardiovascular risk: A report of the American College of Cardiology/American Heart Association Task Force on Practice Guidelines. J Am Coll Cardiol 2014;63:2960-84.

17 van Halm VP, Peters MJ, Voskuyl AE, Boers M, Lems WF, Visser M, *et al.* Rheumatoid arthritis versus diabetes as a risk factor for cardiovascular disease: A cross-sectional study, the CARRE investigation. Ann Rheum Dis 2009;68:1395-400.

18 Zieman S, Kass D. Advanced glycation end product cross-linking: Pathophysiologic role and therapeutic target in cardiovascular disease. Congest Heart Fail 2004;10:144-9.

19 Klein RL, Laimins M, Lopes-Virella MF. Isolation, characterization, and metabolism of the glycated and nonglycated subfractions of low-density lipoproteins isolated from type I diabetic patients and nondiabetic subjects. Diabetes 1995;44:1093-8.

20 Damasiewicz-Bodzek A, Wielkoszyński T. Advanced protein glycation in psoriasis. J Eur Acad Dermatol Venereol 2012;26:172-9.

21 Kaur S, Zilmer K, Leping V, Zilmer M. Serum methylglyoxal level and its association with oxidative stress and disease severity in patients with psoriasis. Arch Dermatol Res 2013;305:489-94.

22 O'Leary DH, Polak JF, Kronmal RA, Manolio TA, Burke GL, Wolfson SK Jr., *et al.* Carotid-artery intima and media thickness as a risk factor for myocardial infarction and stroke in older adults. Cardiovascular Health Study Collaborative Research Group. N Engl J Med 1999;340:14-22.
23 Sparvero LJ, Asafu-Adjei D, Kang R, Tang D, Amin N, Im J, *et al.* RAGE (Receptor for advanced glycation endproducts), RAGE ligands, and their role in cancer and inflammation. J Transl Med 2009;7:17.
24 Papagrigoraki A, Maurelli M, Del Giglio M, Gisondi P, Girolomoni G. Advanced glycation end products in the pathogenesis of psoriasis. Int J Mol Sci 2017;18. pii: E2471.
25 Xiong DD, Zhang M, Li N, Gai JF, Mao L, Li M, *et al.* Mediation of inflammation, obesity and fatty liver disease by advanced glycation endoproducts. Eur Rev Med Pharmacol Sci 2017;21:5172-8.
26 Shoelson SE, Lee J, Goldfine AB. Inflammation and insulin resistance. J Clin Invest 2006;116:1793-801.
27 Chen L, Chen R, Wang H, Liang F. Mechanisms linking inflammation to insulin resistance. Int J Endocrinol 2015;2015:508409.
28 Serrano-Marco L, Barroso E, El Kochairi I, Palomer X, Michalik L, Wahli W, *et al.* The peroxisome proliferator-activated receptor (PPAR) β/δ agonist GW501516 inhibits IL-6-induced signal transducer and activator of transcription 3 (STAT3) activation and insulin resistance in human liver cells. Diabetologia 2012;55:743-51.
29 Papagrigoraki A, Del Giglio M, Cosma C, Maurelli M, Girolomoni G, Lapolla A, *et al.* Advanced glycation end products are increased in the skin and blood of patients with severe psoriasis. Acta Derm Venereol 2017;97:782-7.
30 Micha R, Imamura F, Wyler von Ballmoos M, Solomon DH, Hernán MA, Ridker PM, *et al.* Systematic review and meta-analysis of methotrexate use and risk of cardiovascular disease. Am J Cardiol 2011;108:1362-70.
31 Meerwaldt R, Links T, Graaff R, Thorpe SR, Baynes JW, Hartog J, *et al.* Simple noninvasive measurement of skin autofluorescence. Ann N Y Acad Sci 2005;1043:290-8.
32 Meerwaldt R, Lutgers HL, Links TP, Graaff R, Baynes JW, Gans RO, *et al.* Skin autofluorescence is a strong predictor of cardiac mortality in diabetes. Diabetes Care 2007;30:107-12.
33 Monnier VM, Bautista O, Kenny D, Sell DR, Fogarty J, Dahms W, *et al.* Skin collagen glycation, glycoxidation, and crosslinking are lower in subjects with long-term intensive versus conventional therapy of type 1 diabetes: Relevance of glycated collagen products versus HbA1c as markers of diabetic complications. DCCT skin collagen ancillary study group. Diabetes control and complications trial. Diabetes 1999;48:870-80.
34 Gerrits EG, Lutgers HL, Kleefstra N, Graaff R, Groenier KH, Smit AJ, *et al.* Skin autofluorescence: A tool to identify type 2 diabetic patients at risk for developing microvascular complications. Diabetes Care 2008;31:517-21.
35 Vlassara H, Uribarri J. Advanced glycation end products (AGE) and diabetes: Cause, effect, or both? Curr Diab Rep 2014;14:453.
36 Uribarri J, Woodruff S, Goodman S, Cai W, Chen X, Pyzik R, *et al.* Advanced glycation end products in foods and a practical guide to their reduction in the diet. J Am Diet Assoc 2010;110:911-16.e12.
37 Goldberg T, Cai W, Peppa M, Dardaine V, Baliga BS, Uribarri J, *et al.* Advanced glycoxidation end products in commonly consumed foods. J Am Diet Assoc 2004;104:1287-91.
38 Uribarri J, Peppa M, Cai W, Goldberg T, Lu M, He C, *et al.* Restriction of dietary glycotoxins reduces excessive advanced glycation end products in renal failure patients. J Am Soc Nephrol 2003;14:728-31.
39 Rahbar S, Figarola JL. Novel inhibitors of advanced glycation endproducts. Arch Biochem Biophys 2003;419:63-79.