The AGEs of Psoriasis: A Biomarker for Severity and a Pathogenetic Link to Comorbidities

Advanced glycation end products (AGEs) are highly oxidant compounds derived from non-enzymatic glycosylation reactions of reducing sugars with proteins, lipids or nucleic acids, which become structurally modified with altered functionality (1). Exogenous sources of AGEs include cigarette smoke and components of the diet. AGEs can be ingested with high temperature processed foods and formed as a consequence of high dietary sugar intake. In fact, dietary-induced AGEs have been demonstrated to interfere with many cell functions, contributing to the onset of organ damage in liver (2) AGEs accumulate continuously in human tissues during the entire lifespan and have been involved in the pathogenesis of age-related diseases, such as neurodegenerative diseases, atherosclerosis, diabetes, chronic inflammatory diseases, cancer and human skin ageing (1). AGEs have been associated with arterial stiffness in patients with hypertension and are important enhancers of diabetes complications (3, 4).

AGEs exert their biological actions through binding to a pattern recognition cell surface receptor, RAGE, and triggering several signalling pathways involved in inflammation and tumorigenesis. RAGE is expressed in many cell types, including lymphocytes, macrophages, endothelial cells and keratinocytes, and binds other ligands, such as S100 proteins and high-mobility group box 1 (HMGB1) that have been involved in the pathogenesis of psoriasis. The 2184G allele of a RAGE gene polymorphisms has been associated with psoriasis in patients with a negative history of cardiovascular diseases or diabetes (5), and serum concentrations of AGEs have been found to be elevated in patients with active psoriasis in comparison to healthy individuals, and to return to the normal range in the remission phase (6). This study did not take into account patients' comorbidities, and the serum levels of AGEs were not found to correlate with the Psoriasis Area and Severity Index (PASI).

The present issue of *ActaDV* includes an excellent study and review by Papagrigoraki et al. (7), who conclude that patients with severe psoriasis have accumulation of AGEs in the skin and serum, independent of associated metabolic disorders. They included in their study 40 patients with mild psoriasis (median PASI 4.5), 40 patients with severe psoriasis (median PASI 16.2), 40 patients with severe chronic eczema and 40 healthy individuals. Patients and healthy individuals with psoriatic arthritis, smoking habit, diabetes, dyslipidemia, hypercholesterolemia, hypertension, systemic inflammatory, metabolic or autoimmune disease or under systemic treatment or phototherapy were excluded, and there were no differences in age, sex, body mass index, plasma cholesterol, triglycerides, creatinine, liver enzymes and glucose levels between cases and controls. Serum levels of AGEs correlated well with skin levels and, most interestingly, with psoriasis severity (PASI). In addition, serum levels of soluble RAGE were found to correlate inversely with disease severity in patients with psoriasis.

AGEs are usually measured using skin fluorescence and enzyme-linked immunoassays in serum or plasma, but in most reports both techniques are used separately. The correlation of skin and serum measurements with psoriasis severity suggests that skin fluorescence can be a simple and useful method to study the effect of treatment and comorbidities on AGEs in patients with psoriasis, or to identify those patients with a higher oxidative burden and potential risk to develop cardiovascular or metabolic comorbidities of psoriasis.

Future studies should provide further information on the importance of the smoking habit or diet on the overall levels of AGEs in psoriasis. Obesity is common in psoriasis patients, and one can speculate that the dietary intake of sugars in obese patients is greater than in the normal weight population, even in the absence of diabetes or insulin resistance. If this are the case, the relative contribution of diet to the measured levels of AGEs would be of great interest. As regards diabetes, one of the challenges to prevent the development of complications is to reduce not only the glycaemia levels but also the levels of dietary AGEs. The same strategy applied to patients with severe psoriasis might contribute to control the inflammation and severity of disease, at least in difficult-to-treat patients, and help to prevent cardiovascular and metabolic complications, in patients with severe psoriasis.

Furthermore, AGEs might prove to be a useful biomarker of both systemic and cutaneous inflammation in psoriasis, and therapeutic interventions on the AGE/RAGE pathways might prove to open new perspectives for improved control of both psoriasis and its comorbidities.

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