Skin advanced glycation end products as a screening tool of neuropathy in type 2 diabetes

Aim: To examine the diagnostic utility of skin advanced glycation end products (AGEs) as a screening tool of neuropathy in type 2 diabetes mellitus (T2DM).
Methods: 132 participants with T2DM (88 men; mean age 64.57 years; median diabetes duration 14.5 years) were included. Skin AGEs were measured with AGE reader mu connect (*Diagnoptics*, NL) on the dominant arm and were interpreted as normal vs. elevated. Distal sensorimotor polyneuropathy (DSPN) was diagnosed by the Neuropathy Disability Score (NDS). Cardiovascular autonomic neuropathy (CAN) was diagnosed by cardiovascular autonomic reflex tests (CARTs). In particular, parasympathetic and sympathetic impairment were defined as abnormal expiration to inspiration ratio and abnormal postural hypotension test, respectively.
Results: For DSPN AGEs showed high sensitivity (82.8%) and negative predictive value (NPV) (80.4 %) with moderate specificity (55.4 %). Their agreement with DSPN was fair (Cohen's kappa was 0.366, $p<0.001$). The odds ratio (OR) of abnormal AGEs for presence of DSPN was 5.96 with a 95% CI of 2.62-13.56 ($p<0.001$). For CAN, relatively high sensitivity (75%) and NPV (74.5%) with low specificity (48.7%) have been documented. Their agreement with CAN was fair (Cohen's kappa was 0.218, $p=0.007$). The OR of abnormal AGEs for presence of CAN was 2.85 with a 95% CI of 1.32–6.15 ($p=0.007$). Moreover, AGEs showed relatively high sensitivity (75%) and high NPV (84.3%) with low specificity (43.9%) for sympathetic nervous system impairment. By contrast, for parasympathetic nervous system impairment, high PPV (81%) with sensitivity of 66.7 % and specificity of 55.9% have been found.
Conclusions: Skin AGEs are a potential screening tool of DSPN and CAN in T2DM.

Comments. Chronic hyperglycaemia activates several biochemical pathways and, among others, leads to the formation of AGEs. These latter promote inflammation and impair normal electrical activity in neurones. AGEs may be measured by ELISA, HPLC, mass spectrography, and tissue biopsy or through evaluation of skin autofluorescence. In recent years, their measurement in the skin has attracted considerable interest, because it is non-invasive and accurate. The same authors have previously reported that skin AGEs are increased in the presence of DSPN (Papachristou S et al *J Diabetes Res. 2021;2021:6045677)* and CAN (Papachristou et al *Exp Clin Endocrinol Diabetes, 2022 Nov 7*) in T2DM. Now, they suggest this method as a practical screening tool enabling an easy interpretation (i.e., normal *vs.* abnormal) for the detection of neuropathy in T2DM. Indeed, such binary approach increases simplicity and allows wider usability. Considering the present results, this new screening tool appears particularly useful for the exclusion of DSPN, CAN and sympathetic nervous system impairment (high NPV), as well as for the detection of parasympathetic nervous system impairment (high PPV). The limitations of this work include the smaller number of female than male participants, the absence of nerve conduction study, and the tertiary care setting, which calls for attention when generalising results to primary care. Thus, these findings need validation in larger populations and in the primary care setting. Despite these limitations, the present results are in agreement with prior experience and offer the additional advantage of simplicity for screening purposes. In conclusion, skin AGEs evaluation might represent an easily accessible method in clinical practice to identify the presence of DSPN and CAN with a view to a step-by-step strategy for diabetic neuropathy screening.

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Reference. Papachristou S, Pafili K, Trypsianis G, Papazoglou D, Vadikolias K, Papanas N. Skin advanced glycation end products as a screening tool of neuropathy in type 2 diabetes mellitus. J Diabetes Complications. 2022 Dec;36(12):108356. doi: 10.1016/j.jdiacomp.2022.108356. Epub 2022 Nov 8. PMID: 36395605.

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