

Collagen turnover: a novel marker for cardiac autonomic neuropathy?

Aim: Collagen type IV and III have previously been associated with nerve function. In the present study the authors explored whether markers for collagen IV formation and collagen III degradation were associated with cardiac autonomic and peripheral neuropathy in diabetes.

Methods: The study included a total of 300 participants with type 1 diabetes. Participants were screened for cardiac autonomic neuropathy using cardiovascular reflex tests (2/3 abnormal for confirmed diagnosis) and for peripheral neuropathy using biothesiometry (bilateral vibration sensation threshold > 25 V for diagnosis). Markers for collagen IV formation (PRO-C6) and collagen III degradation (C3M) were obtained in both serum and urine.

Results: The population had a mean diabetes duration of 40.0±8.9 years and a HbA1c of 63±11 mmol/mol. Median serum PRO-C6 was 7.8 (6.2;11.0) ng/ml and C3M was 8.3 (7.1;10.0) ng/ml. Cardiac autonomic neuropathy was diagnosed in 34% of the participants, while peripheral neuropathy was diagnosed in 43%. In adjusted models a doubling of serum PRO-C6 was significantly associated with an odds ratio > 2 for cardiac autonomic neuropathy and an odds ratio > 1 for peripheral neuropathy, with only cardiac autonomic neuropathy remaining significant after additional adjustment for eGFR. A higher serum C3M was also associated with the presence of cardiac autonomic neuropathy, but significance was lost after adjustment for eGFR. Analysis of the urine samples indicated similar associations.

Conclusions: The results indicate an association between markers of collagen turnover and the risk of having cardiac autonomic neuropathy and to a lesser degree peripheral neuropathy.

Comments. The present study shows a previously undescribed association between PRO-C6, a marker for collagen IV formation, and the risk of having cardiac autonomic neuropathy. The findings are of particular interest as they could represent a novel pathophysiological target. The study excels due to its novel finding and substantial number of participants, while its cross-sectional design and crude measure of peripheral neuropathy are its most important limitations in addition to the non-tissue specific nature of the collagen markers. Further longitudinal studies are needed to confirm causality and to establish if the marker precedes other signs of early autonomic nerve damage.

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Reference. Hansen CS, Rasmussen DGK, Hansen TW, Nielsen SH, Theilade S, Karsdal MA, Genovese F, Rossing P. Collagen turnover is associated with cardiovascular autonomic and peripheral neuropathy in type 1 diabetes: novel pathophysiological mechanism? *Cardiovasc Diabetol.* 2023 Jun 29;22(1):158. doi: 10.1186/s12933-023-01891-8. PMID: 37386485; PMCID: PMC10311721.

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