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Apolipoprotein M is associated with cardiac autonomic neuropathy in patients with type 1 diabetes

Aim: Apolipoprotein M (apoM) is an HDL-associated protein that carries Sphingosine-1-Phosphate (S1P). S1P and its receptors, expressed also in human heart, may have a role in the regulation of heart rate variability (HRV). Measurement of S1P needs pre-analytical care and is affected by circadian rhythm. Thus, apoM measurement could be considered as an easier modality to assess S1P levels in clinical practice. This study investigates the association between plasma apoM levels and the risk of cardiac autonomic neuropathy (CAN) in a cohort of patients with type 1 diabetes (T1D).
Methods: 278 participants with T1D without known heart disease were recruited from Steno Diabetes Center Copenhagen from 2010 to 2012 (mean age 54.6 years, 49% male, HbA1c 63.9 mmol/mol, BMI 24.8 kg/m^2). Clinical and biochemical variables were collected. CAN was measured using time and frequency domain indices of HRV (through fast Fourier analysis) obtained from 5-min resting ECG recordings. In addition, three cardiovascular autonomic reflex tests (CARTs) were performed i.e., lying-to-standing, deep breathing and Valsalva manoeuvre). Human plasma apoM was measured using a sandwich-based ELISA.
Results: The prevalence of confirmed CAN was 24%. Patients without vs those with CAN showed increased LDL-cholesterol levels (2.5 vs 2.3 mmol/L), increased eGFR (89.9 vs 74 ml/min/1.73m^2), and reduced plasma apoM levels (1.19 vs 1.3 µmol/l, p=0.03). An increase of apoM plasma levels by 0.1 µmol/l was associated with the presence of CAN also after adjustment for age and gender (Odds ratio 1.11), lipids, blood pressure, alcohol and beta-blockers (Odds ratio 1.14), HbA1c and duration (Odds ratio 1.13), and microalbuminuria (Odds ratio 1.12). In addition, a significant association between higher apoM levels and lower HRV indices was observed.
Conclusions: This study reports an association between increased plasma apoM levels and the presence of CAN in a population of T1D patients. This result is unexpected and in contrast with other findings, given that higher apoM levels were found protective for cardiovascular events and survival and decreased S1P levels were associated with CAN in patients with type 2 diabetes. More insights are needed into the link between apoM, S1P and autonomic function to better determine the S1P-receptor pathway and its possible application in clinical practice.

Comments. The need to improve the diagnosis and the management of CAN is an actual challenge. To find biomarkers as early risk markers for CAN or to identify pathogenetic mechanisms might be a possible way to address this gap. This observational study suggests S1P-ApoM system as a possible pathway to assess the risk of CAN in patients with diabetes. This might have relevant clinical implications given the present or future availability of treatment targeting S1P-receptor or modulating apoM. However, apoM is here used as a proxy for S1P and the effects on cardiac autonomic function of both apoM and S1P might be mediated by complex and not univocal mechanisms whose knowledge may make it possible to reconcile these results with previous data. A validation prospective study could be useful to explore the mechanisms of this association.

Ilenia D'Ippolito

Reference. Safi M, Borup A, Stevns Hansen C, Rossing P, Thorsten Jensen M, Christoffersen C. Association between plasma apolipoprotein M and cardiac autonomic neuropathy in type 1 diabetes. Diabetes Res Clin Pract. 2022 Jul;189:109943. doi: 10.1016/j.diabres.2022.109943. Epub 2022 Jun 8. PMID: 35690270.
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