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Metabolic mechanisms may contribute to cardiovascular autonomic neuropathy in type 1 diabetes

Introduction: Investigations of metabolic mechanisms may present new insight into the pathophysiology, severity, and progression of diabetic microvascular complications. This study explored the potential associations between metabolic pathways, through circulating metabolites and lipids, and cardiovascular autonomic neuropathy (CAN) in people with type 1 diabetes.
Methods: CAN was assessed in 302 persons with longstanding type 1 diabetes with three cardiovascular autonomic reflex tests (lying-to-standing, deep breathing, and Valsalva maneuver), with heart rate and heart rate variability. Based on age-dependent cut-offs, CAN was defined as 2 or 3 pathological tests. Metabolomic profiling was performed using two-dimensional gas chromatography with time of flight mass spectrometry, while lipidomic profiling was performed using ultra-high-performance liquid chromatography quadruple time of flight mass spectrometry.
Results: Sixteen metabolites and one class of lipids were associated with CAN allocated into higher levels of hydroxy fatty acids, tricarboxylic acid cycle, sugar derivatives, and phenols, but lower levels of amino acids and phosphatidylcholines. However, a number of these were dependent on kidney function through estimated glomerular filtration rate.
Conclusions: This study is the first report of associations between CAN and hydroxy fatty acids, sugar derivatives, and phenols, while associations with tricarboxylic acid cycle and amino acids confirm previous reports. Though the study's cross-sectional nature does not allow for conclusions on causality, these metabolites may prove to be modifiable risk factors for CAN in the future.

Comment. The field of omics – it being genomics, transcriptomics, proteomics, metabolomics, or others – has been rapidly developing since the mapping of the human genome in the late 20th century. Though the field is still young, it already shows great potential in providing a deeper understanding of disease mechanisms. In the future, it may help guide precision medicine in multifaceted and complex diseases such as diabetic neuropathies. This is highly needed as even though our understanding of pathogenesis and progression has greatly improved in recent years, we still have no cure for diabetic neuropathy and are left with no other option than to slow progression, manage and alleviate complications and pain.
This study provides new information about the link between cardiovascular autonomic neuropathy and previously unexplored metabolic pathways in a sizable Danish cohort of people with type 1 diabetes. Confirming previous studies about the association with tricarboxylic acid cycle and amino acids, more possible mechanisms are discovered, including sugar derivates that play a role in the polyol or sorbitol pathway, believed to be one of the underlying mechanisms of diabetic neuropathies.
Though the results cannot explain causality and need to be confirmed in other study populations, studies like this are essential in uncovering new aspects that may expand our knowledge about cardiovascular autonomic neuropathy and guide future research. With this in mind, it will be interesting to see if the results can be replicated both prospectively or in cohorts from other countries or continents.

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Reference. Hansen CS, Suvitaival T, Theilade S, Mattila I, Lajer M, Trošt K, Ahonen L, Hansen TW, Legido-Quigley C, Rossing P, Ahluwalia TS. Cardiovascular Autonomic Neuropathy in Type 1 Diabetes Is Associated With Disturbances in TCA, Lipid, and Glucose Metabolism. Front Endocrinol (Lausanne). 2022 Apr 14;13:831793. doi: 10.3389/fendo.2022.831793.

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