

Association between hypoglycaemic glucose variability and autonomic function in type 1 diabetes with impaired hypoglycaemia awareness

Aim: To assess whether Cardiovascular Autonomic Neuropathy (CAN) increases the severity of hypoglycaemic risk in patients with type 1 diabetes (T1D) and impaired awareness of hypoglycaemia (IAH). The primary endpoint was defined as the percentage of time spent in hypoglycaemia in participants with and without CAN.

Methods: Post-hoc analyses of the IN CONTROL trial (two-center, randomized, cross-over, open-label trial performed at the Amsterdam University Medical Centre and the Medical Centre Haaglanden) including 52 patients with T1D, treated with continuous subcutaneous insulin infusion or multiple daily insulin injections, and IAH according to the Gold criteria. HRV was assessed using 5-minute RR-interval recordings from non-invasive ECG recordings (Nexfin®, BM Eye, Amsterdam, the Netherlands). Then, four Ewing cardiovascular reflex tests for CAN were performed: the Valsalva ratio, the 30:15 ratio on standing up, the maximum-minimum heart rate during deep breathing, and postural blood pressure change. Patients underwent a 2-week blinded CGM system (Medtronic, Northridge, CA, USA). Several parameters of glycaemic variability were calculated.

Results: Finally, 40 participants' data were analyzed: age 46.4±11.4 years, 62.5% male, diabetes duration 29±13.5 years, and HbA1c 7.5±0.8%. 35% of all participants were classified as having CAN. All HRV measures (SDRR, RMSSD, LF power, HF power) were significantly lower in patients with CAN compared to those without CAN. The percentage of time spent in hypoglycaemic range was significantly lower in participants with CAN compared to participants without CAN (8.9% vs 12.3%, p=0.015). The hypoglycaemia-specific glucose variability parameter LBG1, the coefficient of variation CV as well as the percentage of time spent in hypoglycaemic range, showed a significant positive association with all four HRV measures.

Conclusion: Hypoglycaemia variability parameters were associated with better cardiovascular autonomic function and a lower prevalence of CAN in patients with T1D and IAH.

Comments. Earlier studies showed that CAN was associated with hypoglycaemia unawareness, with impaired adrenergic responses during hypoglycaemia, with a higher glycaemic variability reflecting hypoglycaemic stress, and with an increased risk of severe hypoglycaemia. These results in contrast show that higher hypoglycaemic exposure was correlated with a better cardiovascular autonomic function. The data suggest that autonomic neuropathy does not seem to further deteriorate hypoglycaemic risk in patients with IAH. The inverse correlation between time in hypoglycaemic range and time in hyperglycaemic range and the association between lower time in hypoglycaemic range and peripheral neuropathy, retinopathy or nephropathy make the Authors suggest that people with IAH spent more time in hypoglycaemia and less time in hyperglycaemia with a saving effect on complications. The discrepancies between the studies in this area call for larger and properly designed studies.

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Reference. Racca C, Bouman EJ, Van Beers CAJ, Smits MM, van Raalte DH, Serné EH. Association between hypoglycaemic glucose variability and autonomic function in type 1 diabetes with impaired hypoglycaemia awareness. *Diabetes Res Clin Pract.* 2022 Jul; 189:109964. doi: 10.1016/j.diabres.2022.109964. Epub 2022 Jun 16. PMID: 35716850.

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