Type 2 diabetes phenotypes and polyneuropathy: a prevalence study in the DD2 Cohort

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Background and aims: Hyperinsulinemia may cause diabetic polyneuropathy (DPN), but large-scale studies are scarce. Three phenotypes of type 2 diabetes (T2D) have recently been proposed: hyperinsulinemic (low insulin sensitivity, high beta cell function), classical (low insulin sensitivity, low beta cell function), and insulinopenic (high insulin sensitivity, low beta-cell function). We aimed to investigate the association of hyperinsulinemia with DPN.
Materials and methods: We included 3,397 recently diagnosed T2D patients prospectively enrolled from general practitioners and outpatient hospital clinics in Denmark, 2010-2015. Insulin sensitivity and beta-cell function were quantified with the HOMA2 model based on fasting serum C-peptide and plasma glucose levels measured at enrollment. DPN was defined as a score of ≥4 on the Michigan Neuropathy Screening Instrument questionnaire sent out median 3 years after study enrollment. We imputed missing values of potential confounders and applied Poisson regression to calculate adjusted prevalence ratios (PR) of DPN.
Results: We identified 900 (27%) hyperinsulinemic, 2,150 (63%) classical, and 347 (10%) insulinopenic T2D patients. Hyperinsulinemic patients had the highest prevalence of central obesity (waist circumference ≥88/102 cm [F/M]; 89% of hyperinsulinemic, 75% of classical, and 36% of insulinopenic) and had more dyslipidemia and hypertension, but less dysregulated HbA1c (≥53 mmol/L; 9%, 16%, 22%). The age-, sex-, and diabetes duration adjusted PR of DPN was 1.44 (95% CI 1.23-1.68) for hyperinsulinemic T2D patients, compared with the classical phenotype. The prevalence remained elevated (1.32 [1.13-1.55]) after further adjustment for waist circumference, dyslipidemia, hypertension, and HbA1c. For the insulinopenic patients, the adjusted PRs of DPN were 0.87 (0.65-1.15) and 1.16 (0.86-1.55), respectively. In spline analyses, both hyperinsulinemia (ie., higher beta-cell function) and lower insulin sensitivity associated with increased prevalence of DPN. The association between increasing hyperinsulinemia and increasing DPN prevalence persisted among patients with low insulin sensitivity (classical or hyperinsulinemic patients). In contrast, among hyperinsulinemic (high beta-cell function) patients, decreasing insulin sensitivity was not associated with DPN.
Conclusion: The prevalence of DPN is increased in T2D patients with the hyperinsulinemic phenotype. Hyperinsulinemia per se is associated with DPN, irrespectively of insulin resistance and other metabolic factors.
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