Patterns of cutaneous nerve fibre loss and regeneration in type 2 diabetes with painful and painless polyneuropathy

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The determinants and mechanisms contributing to the development of diabetic sensorimotor polyneuropathy (DSPN) as a painful or painless entity remain unclear. We examined the degree of cutaneous nerve fibre loss and regeneration in type 2 diabetes patients with painful (DSPN+p), painless DSPN (DSPN-p), and recent-onset diabetes and the corresponding controls.

Skin biopsies from the distal lateral calf were obtained from 32 recent-onset type 2 diabetes patients, 32 type 2 diabetes patients with DSPN-p, 34 patients with DSPN+p and from glucose-tolerant individuals (Control 1: n = 50; Control 2: n = 25). Double immunofluorescence staining for Protein Gene Product (PGP9.5) (pan-neuronal marker) and growth-associated protein-43 (GAP-43) (nerve regeneration marker) was applied to assess intraepidermal nerve fibre density (IENFD), intraepidermal and dermal nerve fibre length (IENFL, DNFL), and the GAP-43/PGP9.5 ratios. DSPN was diagnosed using modified Toronto Consensus (2011) criteria.

After adjustment for age, sex and BMI, IENFD and IENFL were reduced with both markers in recent-onset type 2 diabetes patients and both DSPN groups compared to controls (all $P < 0.05$) and tended to decline further in DSPN+p compared to DSPN-p (PGP: $P = 0.056$, GAP: $P = 0.067$). DNFL did not differ significantly between the groups, but tended to be lower in DSPN+p than Control 2 for GAP-43 ($P = 0.07$). DNFL GAP-43/PGP9.5 ratio was higher in the DSPN groups compared to Control 2 ($P \leq 0.05$) and also higher in DSPN+p compared to DSPN-p ($P = 0.036$). No differences in nerve function were noted between the DSPN-p and DSPN+p groups. Correlation analyses showed distinct inverse associations between the DNFL GAP-43/PGP9.5 ratio and IENFD (PGP9.5: $r = -0.624$, GAP-43: $r = -0.615$; both $P < 0.0001$) in type 2 diabetes patients, but not in control subjects. A similar pattern was seen for correlations between the DNFL GAP-43/PGP9.5 ratio and peripheral nerve function tests.

In conclusion, dermal nerve fibre regeneration is enhanced in both DSPN entities in type 2 diabetes, but to a higher extent in painful than painless DSPN and altogether increases with advancing intraepidermal nerve fibre loss. These data suggest that despite progressive epidermal nerve fibre loss, dermal nerve repair is preserved particularly in painful DSPN, but fails to adequately counteract epidermal neurodegenerative processes.