# NEW ADVANCES IN DIABETIC NEUROPATHY

Pages with reference to book, From 240 To 241

M.T.A. Rehman ( Department of Medicine, Aga Khan University Hospital, Karachi. )

Neuropathy is encountered in about 20% of diabetic patients,[1] It may manifest either as a predominantly sensory neuropathy or a mixed sensory-motor neuropathy. Alternative presentations include autonomic neuropathy, isolated or multiple cranial neuropathy, mononeuritis multiplex or a combination of the above. This complication of diabetes is thought to result from a complex interplay between multiple direct and indirect metabolic consequences of insulin deficiency and hyperglycaemia. [2,3] New knowledge of the pathogenesis of peripheral neuropathy and dysfunction has emerged over the past decade. Green and Sima proved, in animal experiments, that persistent hyperglycaemia activates the poiyi pathway, leading to conversion of glucose to sorbitol, via the enzyme, aldose-reductase. [4] Anders and co-workers have demonstrated that aldose-reductase inhibitor, sorbinil, can improve the neuropathological lesions in diabetic neuropathy, leading particularly to a significant increase in regenerating myelinated fibers. [5] Williamson and colleagues suggested that activation of the polyi pathway was dependent as well on factors other than hyperglycaemia, leading to the process of sorbitol accumulation. [6] In addition to sorbitol accumulation there is a decrease in nerve myo-inositol due to an inhibition of its uptake by the nerve terminal. Myo-inositolis required for the sodium-potassium - ATPase activity and a deficiency leads to increased sodium permeability into neural tissues and hence neural dysfunction. [8] Mayer and Tomlinson[8] have hence postulated that myo-inositol supplements or aldose-reductase inhibitors may prevent or improve diabetic neuropathy. Dyck and co-workers[9] have taken an opposing view by showing that mean myo-inositol levels in sural nerve endoneurium were not decreased in 21 diabetic patients with neuropathy as compared to 9 controls. Also diabetic microvascular disease of the vasa nervosum leading to ischemia of nerves, has been implicated in the pathogenesis of neuropathy. [10,11] There is evidence from in vivo studies that diabetic patients have pronounced hypoxia in nerve tissues. [12] Alternatively or in addition, nerve ischemia may be due to endoneural oedema in sensory nerve fibers which leads to increase in pressure with compression of neurocapillaries, and reduction of its blood flow and hypoxia. [13] Kenuiman et al[14] proposed that the younger the age of onset and the longer the duration of diabetes, the greater the risk of developing neuropathy in insulin dependent diabetes. Neuropathyis along term complication of diabetes. Non-insulin dependent diabetes begins insidiously and can be preceded by a long period of glucose intolerance, and hence neuropathy may be a presenting feature. The question that improved glycaemic control prevents or ameliorates diabetic neuropathy, has been posed for along time. Retrospective studies showed that patients with poor glycaemic control tend to develop neuropathies at an earlier age and are more severely affected than patients with better glycaemic control[15-17]. Also in newly diagnosed diabetes mellitus (insulin dependent) institution of therapy to improve diabetic control results in improved motor conduction velocity. [18,19] Painful diabetic neuropathy has been reported to improve after better glycaemic control using continuous subcutaneous insulin infusion. [20] Further evidence of this comes from a study from Oxford which again demonstrated statistically significant differences in nerve conduction and vibratory threshold after 8 months of intensive glycaemic control as compared to a normally treated group. [21] The balance of evidence suggests that improved glycaemic control is important in improvement of nerve function. As the pathogenesis of diabetic neuropathy becomes known, the prospects of therapy also increase. At present the aldosereductase inhibitors are the focus of attention. But more clinical trials and new drugs are required to bring about a revolution in the treatment of diabetic neuropathy.

**REFERENCES**


1. Ward, J.D. Diabetic neuropathy. Clin. Endocrinol. Metabol., 1972; 1:809-27.
2. Brown, M.J. and Asbury, A.K. Diabetic neuropathy. Ann. Neurol., 1984; 15:2.
3. Dyck, P.J.,Thomas, P.K., Lambert, E.H.arid Bunge, R.P. Peripheral ncuropatby. 2nded. Philadelphia, Saunders, 1984, p.1773, 1810.
4. Greene, D.A., Chakrabarti, S., Lattimer, S.A. and Sima, A.A. Role of sorbitol accumulation and myo-inositol depletion in paranodal swellingoflarge myelinated nerve fibersin the insulin deficient spontaneously diabetic bio.breedingrat. Reversal byinsulin replacement, an aldose reductase inhibitor, and myo-inositol. J. Clin. Invest., 1987; 79: 1479.
5. Anders, A.F. and Sima,A.A. Regeneration and repairof myelinated fibers in sural nervc, biopsy specimens from patients with diabetic neuropathy treated with sorbinil. N. Engi. 3. Med., 1988; 319: 548.
6. Williamson, J.R., Rowold, E. and Chang, K. Sexsteroid dependency of diabetic induced changes in polyl metabolism, vascular and collagen cross-linking. Diabetes, 1986; 35:20.
7. Greene, D.A., Lattimer, S.A. and Sima, A.A. Sorbitol, phosphoinositides and sodium¬potassium. ATPasein thepathogenesis of diabetic complications. N. Engl.J. Med., 1987; 316: 599.
8. Mayer, J.H. and Tomlinson, D.R. Prevention of defects of axonal transport and nerve conduction velocity by oral administration of myo.inositol or an aldose.reductase inhibitor in streptozocin diabetic rats. Diabetologia, 1983; 25:433.
9. Dyck, P.J., Zimmerman, BR., Vilen, T.H., Minneratb, SR., Karnes J.L., Yao, 3K. and Poduslo, J.F., Nerve glucose fructose, sorbitol, myo-inositol and fiber degeneration and regeneration in diabetic neuropathy. N. EngI. J. Med., 1988; 319:542.
10. Dyck, P.J., Karnes, J.L, O'Brien, P., Okazaki, H., Lais, A. and Englstad, J. The spatial distribution of fiber loss in diabetic polyneuropathy suggests ischemia. Ann. Neurol., 1986; 19:440.
11. Johnson, P.C., Doll, S.C. and Cromey, D.W. Patbogenesis of diabetic neuropathy. Ann. Neurol., 1986; 19:450.
12. Newrick, P.6., Wilson, AJ., Jakubowski, 3., Boulton, A.J. and Ward, J.D. Sural nerve oxygen tension in diabetics. Br. Med. 3., 1986; 293: 1053.
13. Tuck, R.R., Scbmelzer, J.D. and Low, PA. Endoneurial blood flow and oxygen tension in the sciatic nerves of rats with experimental diabetic neuropathy. Brain, 1984; 107:935.
14. Kenuiman, M.W., Welborn, T.A., McCann, V.J., Stanton, KG. and Constable, L.J. Prevalence ofdiabetic complications in relation to risk factors. Diabetes, 1986; 35:1332.
15. Fagerberg, S.E. Diabeticneuropathy. A clinical and histological study on the significance ofvascular affections. Acts Med. Scand., 1959; 164: (suppl: 345): 91.
16. Gregersori, G. Diabetic neuropatby. Influence of age, sex; metabolic control, and duration of diabetes on motor conduction velocity. Neurology, 1967; 17:972.
17. Priart, J. Diabetes mellitus and its degenerative complications; a prospective study of 4400 patients observed between 1947 and 1973. Diabetes Care, 1978; 1: 168.
18. Fraser, D.M., Campbell, LW.. and Ewing, D.J. Peripheral and autonomic nerve function in newly diagnosed diabetes mellitus. Diabetes, 1977; 26: 546.
19. Gregerson,G. Variations inmotorconductionvelocityproduced byacute changes in the metabolic state in diabetic patients. Diabetologia, 1968; 4:273.
20. Boulton, A.J., Clarke, B., Drury, J. and Ward, J.D. CSII in management of painful diabetic neuropatby. Diabetes Care, 1987; 5:386.
21. Holman, R.R., Dornan, T.L., Mayon-White, V., Howards-Williams, J., Orde-Peckar, C., Jenkins, L, Steemsons, 3., Rolfe, R., Smith, B., Barbour, D., McPherson, K., Poon, P., Rizza, C., Mann, 3.1., Knight, A.H. and Bron, A.). Prevention of deterioration of renal and sensory-nerve function by more

intensive management of insulin-dependent diabetic patients. A two-yearrandomiaed prospectivestudy. Lancet, 1983; 1:204.