Lipids and diabetic neuropathy: A review

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Article points

1. Diabetic neuropathy is common and is associated with cardiovascular risk factors and increased mortality.
2. Lipids could play an important role in the development of DN.
3. Aggressive treatment of lipids not only prevents cardiovascular disease but also the development of DN.

Key words

- Neuropathy
- Lipids
- Statins

Diabetic neuropathy (DN) is a common complication of diabetes but its exact pathogenic mechanism is not fully understood. Various epidemiological studies have shown that increased age, duration of diabetes and poor glycaemic control are associated with DN. There is increasing evidence that DN is also associated with various cardiovascular risk factors such as adverse lipid profile, hypertension and smoking. Once it is fully established, there is no effective treatment for DN apart from its symptomatic control or treatment of foot ulcers that may develop as a result. Good glycaemic control can prevent the development of DN and recent studies have shown that treatment with fibrates or statins reduce development of DN. Therefore, multi-factorial intervention of cardiovascular risk factors not only reduces cardiovascular morbidity and mortality, but also possibly reduces morbidity from DN.

Diabetic neuropathy (DN) is one of the common complications of diabetes that can lead to devastating consequences such as foot ulcers and amputations. The prevalence of DN varies a great deal depending upon the type of population studied and criteria used to define it. In the Rochester Diabetic Neuropathy Study, DN affected almost 60% of those studied but it was symptomatic only in approximately 15% (Dyck et al, 1993). In a cohort of 4400 people, Pirart observed that the prevalence of DN increased from 7% within 1 year of diagnosis to 50% for those with diabetes for more than 25 years (Pirart, 1978). Despite being very common, the exact pathogenesis of DN is not fully understood, although a mixture of vascular defects with metabolic abnormalities is believed to cause the nerve damage (Cameron et al, 2001).

Cardiovascular risk factor and diabetic neuropathy

It is well established that poor glycaemic control, old age and a longer duration of diabetes are associated with DN (DCCT, 1993; Maser et al, 1996; Tesfaye et al, 1996; Adler et al, 1997; Allen et al, 1997; Forrest et al, 1997; Solders et al, 1997). In recent years, cardiovascular risk factors have also been increasingly shown to be associated with the development of DN. In one study, the risk of developing DN was more than three times greater in people with type 1 diabetes who smoked than those who did not, but this was not a significant risk factor in type 2 diabetes (Mitchell et al, 1990). The EURODIAB study also found smoking to be significantly associated with DN (Tesfaye et al, 2005). Hypertension has been associated with the development of DN in the Pittsburgh Epidemiology of Diabetes Complications Study (Forrest et al, 1997). Raised blood pressure as a risk factor for the development

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of DN has been observed by other studies as well (Maser et al, 1996; Tesfaye et al, 2005). Some studies have shown this to be significantly more common in males than females (DCCT, 1988). In a recent paper, Tesfaye et al demonstrated an association between various cardiovascular risk factors and the development of DN (*Table 1;* Tesfaye et al, 2005).

Neuropathy has been associated with increased mortality (Forsblom et al, 1998). In a prospective study of 134 people with type 2 diabetes followed for 9 years, 38 individuals (29 %) died during the follow-up period – the majority of whom (68 %) died from cardiovascular disease. In a multiple logistic regression analysis, macroangiopathy ($P = 0.004$), neuropathy ($P = 0.007$), HbA_{1c} ($P = 0.018$) and albumin excretion rate ($P = 0.016$) were independent risk factors for death. The deceased had higher cardiovascular risk factors and higher HbA_{1c} values at baseline (Forsblom et al, 1998).

Lipids and diabetic neuropathy

Many studies have shown lipids to be a risk factor for the development of DN. One population-based study of 239 people with type 1 diabetes found significant associations between serum triglycerides and lipoprotein(a), and the sensory threshold for vibration, electric current perception and pain (Lithner et al, 1995). Similarly, the EURODIAB IDDM complication study demonstrated that raised lipids are associated with DN (Tesfaye et al, 1996) and, more recently, that they are a risk factor for the development of DN (Tesfaye et al, 2005; Rajbhandari et al, 1999). The higher mortality in people with type 2 diabetes and neuropathy compared with people without neuropathy (57 % versus 23 %; $P < 0.001$) could possibly be due to these cardiovascular risk factors (Forsblom et al, 1998). On the other hand, another study did not find any association between lipids and DN (Maser et al, 1996). Maser and colleagues examined the association between various lipids and lipoprotein(a) concentrations, and large sensory nerve fibre function. This was assessed by vibratory thresholds in a group of 91 individuals. In multivariate analyses, no independent relationships of high-density lipoprotein, low-density lipoprotein, cholesterol, triglycerides and lipoprotein(a) were found.

Treatment of lipids and diabetic neuropathy

There has been paucity of data on whether or not treatment of lipids improves DN. Statins are the treatment of choice for hyperlipidaemia. They appear to exert beneficial effects on vascular function independent of cholesterol lowering (Sorrentino and Landmesser, 2005). On the other hand, statins can cause neuropathy as a side effect. In one study, treatment with statins for 2 or more years was observed to increase the risk of developing polyneuropathy 26-fold (Gaist et al, 2002). In studies using rats with diabetes, rosuvastatin treatment was shown to correct neuropathy and improve blood flow in small blood vessels. Rosuvastatin did not alter plasma cholesterol in diabetic animals but significantly lowered triglycerides at high doses (Cameron et al, 2003). In a small study in the US, this finding has been replicated in 18 people with DN. They were treated with rosuvastatin 10 mg daily for 18 weeks. This improved neurophysiological parameters of DN and skin perfusion (Parson et al, 2007).

The Fremantle Diabetes Study in Australia demonstrated important evidence of a

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1. Many studies have shown lipids to be a risk factor for the development of diabetic neuropathy.
2. One population-based study of 239 people with type 1 diabetes found significant associations between serum triglycerides and lipoprotein(a), and the sensory threshold for vibration, electric current perception and pain.
3. The higher mortality in people with type 2 diabetes and neuropathy compared with people without neuropathy could possibly be due to cardiovascular risk factors.
4. There has been paucity of data on whether or not treatment of lipids improves diabetic neuropathy.

Table 1. Risk factors for neuropathy after adjustment for glycosylated haemoglobin values and duration of diabetes (adapted from Tesfaye et al and reproduced with kind permission from *NEJM*).

Variable	Odds ratio (95 % CI)	P value
Total cholesterol (mmol/l)	1.26 (1.10–1.45)	0.001
Low-density lipoprotein cholesterol (mmol/l)	1.22 (1.03–1.45)	0.02
Triglycerides (mmol/l)	1.35 (1.16–1.57)	<0.001
Body mass index	1.40 (1.22–1.61)	<0.001
History of smoking	1.55 (1.17–2.04)	<0.001
Hypertension	1.92 (1.30–2.82)	<0.001
Microalbuminuria or macroalbuminuria	1.48 (1.07–2.04)	0.02
Cardiovascular disease	2.74 (1.68–4.49)	<0.001

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1. Observational data provide evidence that therapy with either a statin or fibrate protects against the development of diabetic neuropathy, independent of the effect of these drugs on serum lipids.
2. Aggressive treatment of lipids, either with a statin or fibrate, will not only improve cardiovascular outcome but will also retard the development of diabetic neuropathy, and possibly foot ulcers and amputations.

beneficial effect of statin use for the treatment of DN. The study investigated 1294 people for a duration of 4 years who had type 2 diabetes. Follow up indicated that 31 % had peripheral neuropathy at baseline and many traditional risk factors such as age, duration of diabetes and poor diabetes control were associated with DN. However, the use of fibrates reduced the prevalence significantly by 70 %. In this cohort, fibrates and statins were used only by 3.5 % and 6.8 % of individuals, respectively. By November 2001, a sub-group of 531 people had attended six comprehensive annual assessments during the 5 years of follow up and fibrate and statin use increased to 10.4 % and 36.5 %, respectively. In this sub-group, for those who developed new-onset DN during follow up, statins and fibrates reduced the risk by approximately 35 % and 48 %, respectively. These observational data provide evidence that therapy with either a statin or fibrate protects against the development of DN, independent of the effect of these drugs on serum lipids (Davis et al, 2007).

Conclusion

Diabetic neuropathy is common and is associated with various traditional cardiovascular risk factors such as hypertension, lipids and smoking. It is possibly because of these associations that people with diabetic neuropathy have a higher risk of mortality. Studies have shown that aggressive treatments of multiple risk factors not only prevent microvascular complications of diabetes but also prevent death and macrovascular complications by almost 60 % (Gæde et al, 2008). Aggressive treatment of lipids, either with a statin or fibrate, will not only improve cardiovascular outcome but will also retard the development of diabetic neuropathy, and possibly foot ulcers and amputations. ■

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