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Lipid profile as a predictor of Neuropathy: The Sheffield Prospective Diabetes Study.

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Abstract

Background : Despite being a very common complication, the aetiology and potential risk factors of diabetic neuropathy (DN) have not been clearly determined in a prospective study. Aims: The aim of Sheffield Prospective Diabetes Study was to identify the abnormalities of physiological, biochemical, haemorrhelogical and cellular function for complications of diabetes in type 1 diabetes.

Materials and Methods: 66 newly diagnosed type 1 diabetic subjects (mean age 31± 9(SD) duration (3 years ± 2) were identified and followed for 9 years. They had detailed neurological assessment (symptoms and signs score, nerve conduction, vibration perception threshold, warm thermal discrimination threshold and autonomic function tests) and blood samples taken for detail biochemical and haemorrheological analysis at base line and at follow up.

Results: At the 9 years follow up, 51 subjects were studied of whom 18 were found to have DN using Dyck's criteria. As expected subjects with DN had significantly higher (p <0.01) mean HbA1 over 9 years of follow up (11.8% vs 9.8%), but it was not significantly different at base line (10.2% vs 8.9%; p= 0.37). In addition, total cholesterol and LDL cholesterol at baseline were found to be risk factors for the development of neuropathy (5.9 vs 4.7 mmol; p=0.01 and 3.7 vs 2.8 mmol; p=0.03 respectively).

Conclusions: This prospective study confirms the findings of recent large epidemiological studies linking cardiovascular risk factors to the development of DN, and perhaps suggest a vascular aetiology for DN. Improvement of potentially modifiable risk factors for neuropathy may be useful for the development of risk reduction strategies.

Introduction:

The pathogenic mechanism leading to Diabetic neuropathy (DN) in human is not fully understood. Animal studies have established the presence of a number of metabolic abnormalities such as oxidative stress, sorbitol accumulation, PKC activation, accumulation of advanced glycated products in DN.[4] Similarly vascular abnormalities such as endoneurial and epineurial vessels changes, nerve hypoxia etc have also been demonstrated. [8] Similar findings have also been demonstrated in human DN.[9]

Epidemiological and prospective studies have identified hypertension[6], increasing age, duration of diabetes and poor glycaemic control [1] as a significant risk factor for the development of DN. There has been association between lipids and DN but there is still a paucity of well-conducted prospective study in this field.

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Sheffield Prospective diabetes study was started with the aim of identifying risk factors associated with the development of diabetic complications in type 1 subjects. This study was approved and funded by Diabetes UK.

Methods:

In this prospective observational study, sixty-six (25 Females) newly diagnosed Type 1 diabetes subjects (mean age 31 - 9(SD) duration (3 years -2) were recruited from a busy diabetes clinic. All consecutive patients who were diagnosed with type 1 diabetes within the last 5 years were approached when they came to the diabetes clinic. Subjects were deemed to have type 1 diabetes if the age at diagnosis was less than 40 and needed insulin within six months of diagnosis. Only those subjects who agreed for detailed neurophysiological examination and long term follow up were included in the study. Subjects who were likely to leave the area, such as university students were excluded. They had clinical neurological assessment performed by neurological symptoms questionnaire and neurological examination. Nerve conduction velocity of median motor, median sensory, peroneal motor and sural sensory nerves was measured at 22 0C using Dantac 2000.[13] For qualitative sensory tests, vibration perception threshold over the great toe was measured using neurothesiometer and warm thermal detection threshold over the dorsum of right foot using thermo-aesthesiometer. Cardiac autonomic function tests were performed using O'Brien protocol. They also had fasting lipid profiles (serum cholesterol, fasting triglycerides, HDL cholesterol and LDL cholesterol) and HbA1c measured. The overall diabetes control (mean HbA1) was measured from the laboratory database by calculating the mean of all HbA1 performed over the study period.

They were treated in diabetes clinic as any other patients without any active intervention. At 9 years they were again invited for detailed follow up as above. Only 51 subjects (77%) attended for follow up as 15 patients had moved out of the area or refused to attend for detailed neurophysiologication (Figure 1). Diagnosis of diabetic neuropathy was made using Dyck's criteria (Dyck 1988).

Results:

At baseline visit 14 (21.2%) out of 66 subjects had evidence of neuropathy on detailed neurophysiological examination. Out of 52 subjects without neuropathy (NN) at baseline, 42 were followed up and 9 subjects (21.4%) developed new onset DN. At 9 years visit 33 subjects (64.7%) did not have neuropathy (NN) and 18 subjects (35.3%), 9 new and 9 established subjects, had DN.

When the lipid levels of 18 subjects with DN was compared with 33 subjects without neuropathy, the levels were raised in all visits (table 1). As expected the overall control over 9 years was poor in DN subjects (mean HbA1 11.8 +/- 2.1% vs 9.8 +/- 1.9%; $p < 0.01$) however this was not statistically significant on the first visit (10.2 +/- 3.2% vs 8.9 +/- 3.0%; p= 0.37).
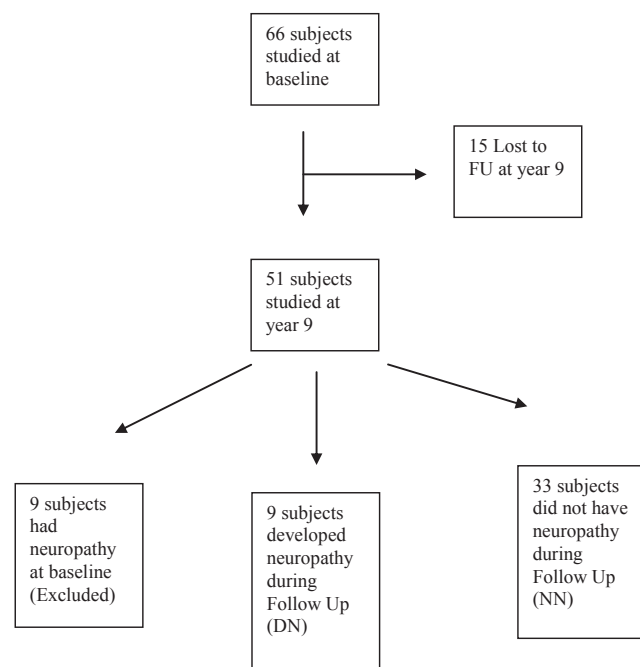

Figure 1: Flowchart of study

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Table 1: Lipid profile of subjects who have diabetic neuropathy at 9 years follow up in comparison to subjects who did not have neuropathy.

		Non-Neuropath		Diabetic Neuropathy		
		Mean	SD	Mean	SD	*p* Value
Triglyceride	Initial Visit	1.30	1.38	1.63	0.84	0.03
	Final Visit	1.06	0.45	1.89	1.44	0.05
Cholesterol	Initial Visit	4.73	1.12	5.57	1.18	0.02
	Final Visit	4.99	0.81	5.76	1.08	0.02
HDL Cholesterol	Initial Visit	1.36	0.34	1.29	0.47	0.34
	Final Visit	1.33	0.35	1.34	0.46	0.84
HDL / Total cholesterol Ratio	Initial Visit	3.67	1.40	4.71	1.53	0.01
	Final Visit	3.97	1.25	4.69	1.53	0.12
LDL Cholesterol	Initial Visit	2.83	1.08	3.55	1.06	0.02
	Final Visit	3.22	0.89	3.57	0.83	0.24

Nine subjects who were NN at first visit developed DN during follow up. In order to look into risk factors for the development of DN, the baseline lipid profiles of these subjects were compared with 33 NN subjects. We found that total cholesterol and LDL cholesterol was significantly raised in this group at baseline with a trend for elevated triglyceride and HDL / Total cholesterol ratio (table 2). There were no significant differences in the overall diabetes control at baseline between these groups (11.1 +/- 4.3% vs 8.9 +/- 3.0%; p= 0.15), however during follow up, the 9 year's mean HbA1, was raised (12.0 +/- 2.3% vs 9.8 +/- 1.9%; p=0.01). The baseline lipid profiles of subjects lost to follow up was statistically no different to those followed up for 9 years.

Table 2: Baseline lipid profiles of subjects who developed new onset diabetic neuropathy during follow up in comparison to those subjects without diabetic neuropathy

	Non - Neuropathy		New Diabetic neuropathy		
	Mean	SD	Mean	SD	*p* Value
Triglyceride	1.30	1.38	1.69	0.91	0.08
Cholesterol	4.73	1.12	5.88	1.06	0.01
HDL Cholesterol	1.36	0.34	1.42	0.55	0.78
HDL / Total Cholesterol Ratio	3.67	1.40	4.59	1.47	0.06
LDL Cholesterol	2.83	1.08	3.70	0.97	0.03

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Discussion:

Previous studies have shown association of lipids to DN. In Eurodiab study Tesfaye et al[19] have shown baseline triglycerides to be associated with neuropathy and have shown both triglycerides and cholesterol to be a risk factor for the development of DN.[5] On the other hand Spallone et al [17] did not find any relation between autonomic neuropathy and lipids. Similarly Maser et al [14] did not find any relation between lipids and vibration threshold. In a recent epidemiological study in young people with diabetes, risk factors for neuropathy in Type 1 DM were older age, longer diabetes duration, smoking, increased diastolic blood pressure, obesity, increased LDL cholesterol and triglycerides, and lower HDL cholesterol. In youth with Type 2 DM, risk factors were older age, male sex, longer diabetes duration, smoking, and lower HDL-c.[11] Our study shows that at baseline both total cholesterol and LDL cholesterol is significantly elevated in subjects who later developed DN. Both total cholesterol and fasting triglycerides levels were significantly raised in subjects with Diabetic neuropathy. Microvascular abnormalities is thought to be the aetiology of neuronal damage.[18] It is possible that similar to hypertension, lipids also contribute to both macrovascular and microvascular complications. The elevated lipids may be in part responsible for reported raised mortality in diabetic neuropathy.[7]

The HbA1 was not statistically different between these two groups at base line, although the mean HbA1 was higher in subjects who later developed DN. The overall control of diabetes was poor in DN group during the 9 year follow up. We did not find any difference between the HDL levels in these two groups. This may be due to both male and female subjects being pooled together. HDL is higher in female subjects. We did not analyse the data separately as the numbers were smaller.

Elevated lipids have been associated with other microvascular complications of diabetes. Triglycerides has been shown to be a risk factor for the development of proliferative diabetic retinopathy.[2] In subjects with diabetic nephropathy, Zimmermann et al[20] demonstrated significantly higher concentrations of LDL-cholesterol, triglycerides and lower concentrations of HDL-cholesterol. In diabetic nephropathy deterioration of renal function has been retarded by LDL plasma apheresis.[16] Similarly HMG Co A reductase inhibitors have been shown to reduce the deterioration in renal function in experimental diabetic nephropathy[10,12], however, the mechanism is thought to be independent of its lipid lowering effect. Therapy with a statin or a fibrate was shown to have protective effect against the development of diabetic peripheral sensory neuropathy [3, 15]

Conclusion:

This prospective study confirms the findings of recent large epidemiological studies linking cardiovascular risk factors to the development of DN, and perhaps suggest a vascular aetiology for DN. Improvement of potentially modifiable risk factors for neuropathy may be useful for the development of risk reduction strategies.

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