Original article

F-wave alterations in diabetic polyneuropathy and their association with diabetic dyslipidaemia

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Abstract:

Introduction: Emerging concepts evince the active role of dyslipidaemia in the development of diabetic neuropathy. Recent data have added a new perspective to the pathogenetic mechanism and the therapeutic care in diabetes in the form of hyperlipidaemia. The present study has hence, attempted to detect diabetic neuropathy by F wave studies which are reportedly sensitive and early neurophysiological indicators and an association of the status of the lipid profiles and ratios in type 2 diabetes with the presence of neuropathy.

Methods: Lipid profile and ratios were determined in 50 type 2 diabetics and the mean values compared with 60 age and sex-matched controls by unpaired t test. F wave study was performed and analysed among the two groups by unpaired t test. $p<0.05$ was considered statistically significant.

Results: A statistically significant difference was observed in the lipid profiles and the ratios between the groups. F wave study detected neuropathy with F wave minimum latency, F wave mean latency, chronodispersion and persistence as useful variables revealing significant alterations among the diabetics.

Conclusion: F wave parameters reveal significant alterations in diabetic neuropathy. Significantly deranged lipid profiles and atherogenic ratios among type 2 diabetics indicate the concurrence of atherogenicity and neuropathy, necessitating the assessment of the lipidaemic status of the patients besides detection of neuropathic signs.

Key words : Diabetic neuropathy, dyslipidaemia, F wave, lipid profile.

Introduction

Diabetic neuropathy (DPN) is the most common complication associated with diabetes mellitus with lifetime prevalence of approximately 50% [1-5]. DPN is a leading cause for disability owing to foot ulceration and amputation, gait disturbance, and fall-related injury [4-7]. Poor quality of life and increase in the health-costs are the sequelae [8].

NCS (Nerve conduction study) is regarded as the standard for DPN diagnosis [9, 10]. The suggested underlying mechanisms have been the long-standing hyperglycemia, associated metabolic derangements (increased polyol flux, accumulation of advanced glycation end products, oxidative stress, and lipid alterations among other metabolic abnormalities). Recent clinical data however, add a new perspective to the pathogenetic mechanism and the therapeutic care. Over the course of years of follow-up, it was not glycaemia, but hypertension, serum lipids, and body mass index were independently associated with the risk of developing diabetic neuropathy [11-16].

It has even been suggested in another similar study that the only clinical parameter that correlated with rapid progression of diabetic neuropathy was elevated plasma triglycerides [17].

New hypothesis hence, describes that increased levels of plasma lipids, either causative of or subsequent to the development of diabetes, act in concert with both oxidative stress and glucose to produce peripheral sensory neuron and microvessel injury, leading to diabetic neuropathy. Hypertriglyceridemia has been associated with subclinical peripheral neuropathy even in the absence of diabetes. Hyperglycemia hence can be hypothesised to accelerate the change if developed later on [18].

These emerging ideas of the important contributory role of dyslipidaemia in the development of diabetic neuropathy also explain the earlier incidence of diabetic neuropathy in patients with type 2 compared to type 1 diabetes. Dyslipidaemia develops later in the course of type 1 diabetes, and these abnormal lipid profiles coincide with the delayed onset and progression of diabetic neuropathy [19, 20].

Diabetes Mellitus represents the form of metabolic neuropathies which are characterised by diffuse lesions in the peripheral neuronal structures (diffuse demyelinating neuropathies) involving the proximal length of the nerve also. Hence, F wave latencies allow a better and sensitive assessment as conventional nerve conduction studies do not have access to the more proximal portions of the nerve involved. The advantage of F-wave methodology in the detection of peripheral neuropathies is that the F-waves have been reported to be clinically significant, and measurable changes even before conventional nerve conduction studies are informative. This might be due to the fact that the slowing of nerve conduction is accentuated by F waves travelling for long distances over the entire length of the nerve. Despite the fact that diabetes results in diffuse involvement of the nerves, yet distal segments of the nerves have been suggested to be more commonly involved in diabetic peripheral neuropathy. F wave study has still been proved to be a very sensitive method in view of latency, chronodispersion and amplitude of the response [21, 22].

Also, F wave changes have even been suggested as first and the only neurophysiological indicators in early diabetic neuropathy [23-25].

The present study encompasses the evaluation of F wave parameters besides the latency; the usefulness of chronodispersion, persistence and F wave amplitude has been intended to be assessed in the diabetic peripheral neuropathy.

Interestingly, F wave alterations have been found to be associated with diabetic dyslipidaemia in some literatures [26]. Such correlation reflects the fact that the neuropathic signs and symptoms or the presence of subclinical neuropathy co-exists with atherogenicity. Substantial evidence regarding this association is yet not in abundance. Also, atherogenic lipid indices are reported to be the predictors for atherosclerosis in type 2 diabetes mellitus but not for neuropathy in some studies [27, 28]. The presence study hence was planned to find out the association between the F wave parameters and dyslipidemic status (lipid profiles and the atherogenic ratios) in type 2 diabetes. The study attempts to test the hypothesis that there is a co-existence of preclinical atherosclerosis with the signs of peripheral neuropathy in diabetic patients.

Materials and methods

We studied 50 patients with type 2 diabetes (28 males and 22 females) (mean age: 55±4.0 years), with and without clinical evidence of peripheral neuropathy. 60 age and sex-matched healthy subjects were enrolled for the study as controls. It was a case-control study. Approval from the institutional ethics committee was obtained to carry out the research work. A written informed consent was obtained before the study. A careful

neurological examination was performed for every subject. None of the patients were on lipid lowering agents. Hypertensive patients were on antihypertensive agents and with controlled levels of blood pressure.

Inclusion criteria:

All patients with diabetes mellitus type 2, (proven by recent blood glucose studies) constituted the study group while control group included the healthy subjects with comparable age-group and gender ratio with normal neurological examination and normal metabolic profile.

Exclusion criteria:

Patients on lipid-lowering agents and those with peripheral nervous system disorders unrelated to diabetes.

The diagnosis of diabetes mellitus was based on World Health Organization (WHO) criteria, i.e. Fasting blood glucose (FBG) ≥126 mg/dL and 2-hour post- prandial blood sugar levels of ≥200 mg/dL. The complications were based on ECG findings, fundus examination, microalbiminurea and the presence of diabetic ulcers. Determination of glucose and lipid profile was done by fasting venous sample of blood. Fasting glucose, glycosylated haemoglobin (HbA1c), serum total cholesterol, serum triglycerides and high-density lipoprotein (HDL) were measured using commercially available kits on spectrophotometer. [TG]/5 gave the estimate of VLDL-cholesterol. Low-density lipoprotein (LDL) was calculated by Friedewald equation {LDL = TC − (HDL + VLDL)}. All values were expressed in mg/dL. Atherogenic lipid ratios included were as follows: Castelli's Risk Index-I (CRI-I)=TC/HDL-c, Castelli's Risk Index-II (CRI-II) = LDLc/HDL-c, Atherogenic Coefficient (AC) = (TC– HDLc)/HDL-c [29]. Atherogenic Index of Plasma (AIP) was calculated as log (TG/ HDL-c) [30]. The atherogenic index of plasma (AIP), defined as logarithm of the ratio of plasma concentration of triglycerides to high-density lipoprotein cholesterol, has recently been proposed as a predictive marker for plasma atherogenicity and is positively correlated with cardiovascular disease risk [31]. Atherogenic coefficient (AC) ratio was calculated as (TC- HDL-c)/HDL-c) [29].

Recording of F-response

F wave parameters were recorded on Allengers Scorpio-EMG, EP, NCS software in Neurophysiology laboratory, MMIMSR, Mullana, Ambala. 20 stimuli at the rate of 0.5 Hz with stimulus duration of 0.2 milliseconds were given. Supramaximal stimulus intensity was 25 percent above maximal. F response was recorded from median and tibial nerves. F wave parameters namely, F wave minimum latency, F wave mean latency, persistence, chronodispersion, F wave mean amplitude and F/M amplitude ratio were determined and expressed as mean ± standard deviations. Mean values of F wave parameters were compared using unpaired student's t test.

Results

Table 1 shows the salient features compared among the controls and the diabetics. Mean age among the two groups did not differ significantly ($p>0.05$). Diabetics presented with complications and associated ailments as nephropathy, ischaemic heart disease, hypertension and diabetic ulcers. Lipid profile changes in terms of serum triglycerides, HDL-c, LDL-c, VLDL-c were found to be statistically significant ($p<0.0001$) among the two groups. All the atherogenic ratios studied, were significantly altered ($p<0.0001$) (table 2).

F wave study revealed the derangements of the majority of the parameters studied. Median and tibial F wave minimum latency, mean latency and persistence while median F wave chronodispersion varied significantly ($p<0.0001$) in the diabetics. F wave mean amplitude and F/M amplitude ratio were not statistically significantly different among the two groups ($p>0.05$) (table 3). Median motor and sensory and tibial motor nerve conduction

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velocities reduced among the diabetics (figure 1). However, only tibial MNCV could be found to be significantly reduced ($p<0.05$).

Table 1: Demographic profile and other salient characteristics of the study

	Controls(60)	**Diabetic subjects (50)**
Mean age (years) (mean±SD)	53±3.0	55±4.0
Gender ratio (M:F)	32:28	28: 22
Hypertension (No.) (%) of subjects) *	4 (6.66%)	10 (20%)
Ischaemic heart disease (No.) (%)of subjects) *	1 (1.66%)	10 (20%)
History of smoking (No.) (%) of subjects)*	5 (8.33%)	12 (24%)
Nephropathy (No.) (%) of subjects) *	1 (1.66%)	16 (32%)
Diabetic ulcers/foot (No.) (%) of subjects) *	0 (0%)	26 (52%)
Glycosylated haemoglobin (%)*	5.9	10.65
Fasting blood glucose(mg/dL) *	100.6	199.48

**p<0.05 for the difference between controls and the diabetics (unpaired t test).*

Table 2: Lipid profile and atherogenic ratios among controls and diabetics

Lipid profile (Mean ±SD)	**Controls**	**Diabetics**
TC (mg/dL)	198.8±11.0	202.8±12.1
TG (mg/dL) *	130.8±9.2	140.9±8.4
HDL-c (mg/dL) *	58.2±2.3	37.3±2.01
LDL-c (TC − (HDL + VLDL) (mg/dL) *	114.44±5.9	137.32±6.2

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VLDL(TG/5) *	26.16±1.84	28.18±1.0
Castelli's Risk Index-I (TC/HDL-c) *	1.74±0.16	5.44±0.23
Castelli's Risk Index-II (LDLc/HDL-c) *	1.97±0.15	3.68±0.16
Atherogenic Coefficient (AC) (TC–HDLc)/HDL-c) *	2.42±0.6	4.44±0.98
Atherogenic index of plasma (AIP) log (TG/ HDL-c) *	0.35±0.06	0.58±0.073

TC: Total cholesterol, TG: Triglycerides, HDL-c: High density lipoprotein-cholesterol, LDL-c: Low density lipoprotein-cholesterol, VLDL: Very low density lipoprotein-cholesterol.

** p<0.0001 for the difference between diabetics and the controls (by unpaired t test).*

Table 3: F wave study among controls and diabetics

	F wave parameters			
	Median		Tibial	
	Controls	Diabetics	Controls	Diabetics
F wave minimum latency (msec)	24.25±4.23	29±5.7*	44.62± 10.2	52±11.34*
F wave mean latency (msec)	26.23±4.45	30±4.7*	46.23±9.16	54±10.45*
Persistence (%)	89.23±11.2	78.67±13.54*	90±7.13	80.23±8.13*
Chronodispersion (msec)	7.01±4.24	10.2±5.6*	6.18±2.4	7±3.2
F wave mean amplitude (µv)	310.18±150.3	300.6±170.5	220±85.2	200±98.56
F/M amplitude ratio	3.85±1.52	3.45±1.7	4.7±1.23	3.99±2.2

** Both median and tibial F wave minimum latency, mean latency and persistence while only median F wave chronodispersion varied significantly (p<0.0001) in the diabetics (unpaired t test).*

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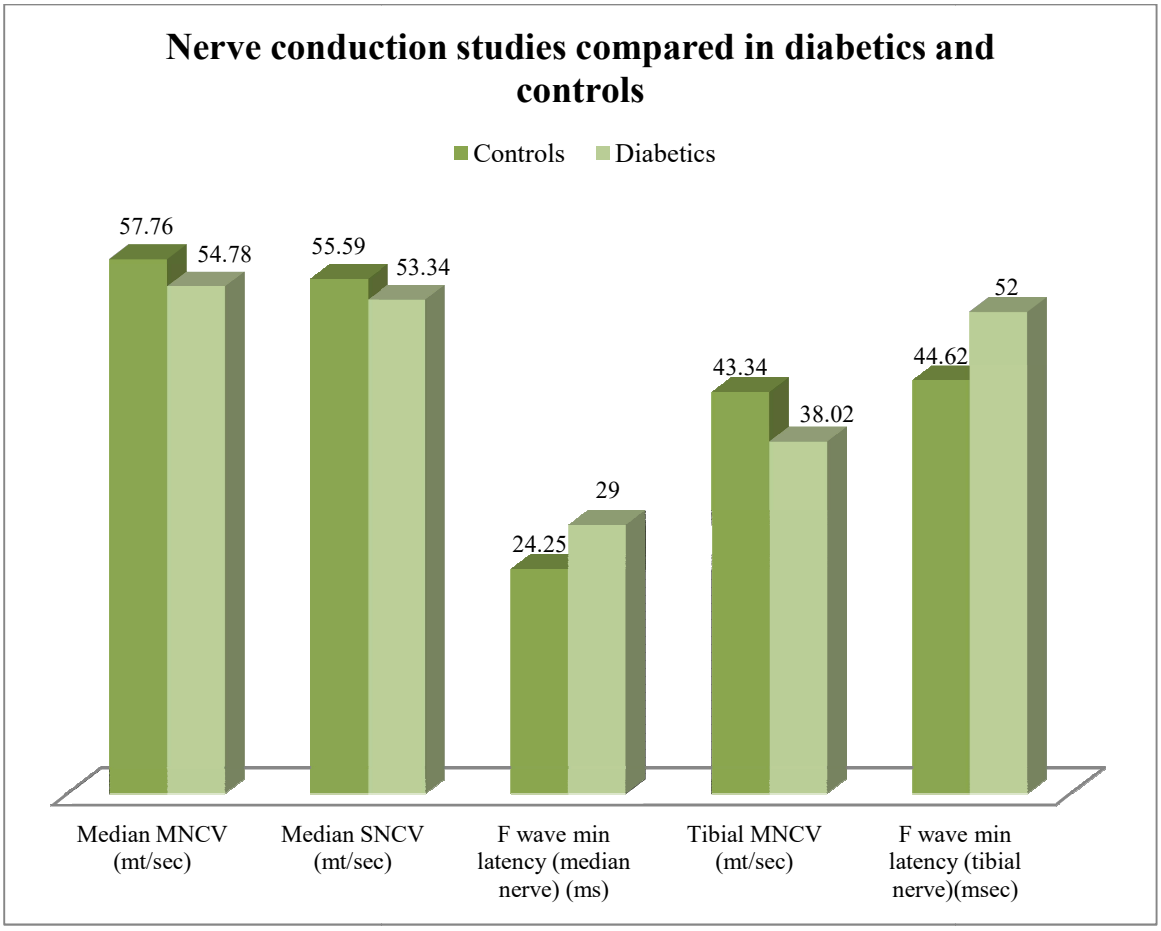

Figure 1: Median MNCV and SNCV, Tibial MNCV and F wave minimum latency among controls and the diabetics

Discussion

Elevated atherogenic ratios and deranged lipid profiles in the diabetics as found in our study reflect the association of atherogenicity and hence the macrovascular complications with diabetic neuropathy. The association is in line with the previous similar study by PA Khanam et al., 2017 [32]. Significant association of TG and HDL-c with high risks of neuropathy have also been reported earlier in a study [33]. Although our study observed significant differences in the lipid profiles as well as the atherogenic ratios, majority have emphasised the greater role of atherogenic ratios which are reported to be varied early as compared to lipid profile measurements and are more valuable and sensitive markers for atherogenicity [26].

F wave study among the diabetics in the present study revealed statistically significant differences in the minimum latency, mean latency, chronodispersion and the persistence, demonstrating the sensitivity of the test. Among the various parameters, F wave minimum latency has been most extensively studied and reported as a sensitive parameter as compared to motor nerve conduction velocity in previous studies also [34, 35].

Another similar study reported that F-waves of the tibial and fibular nerves were the most sensitive measures to detect subclinical or overt diabetic polyneuropathy [36].

In the present study, we also observed significant alterations in F wave mean latencies and persistence for both median and tibial nerve and chronodispersion in upper limb in diabetics as compared to controls which suggest

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the usefulness of the other less commonly employed F wave parameters. Studies in the past also support their importance in adding value to the basic F wave studies in detecting the polyneuropathies [37].

Significantly deranged lipid profile and ratios in the diabetics in the present study validate the role of hyperlipidaemia in the development of the neuropathic signs. The possible mechanisms underlying the impairment of nerve functions by hyperlipidaemia have been speculated to be multiple and are not suggested to influence independently, but interact with each other.

One of the suggested mechanisms is intracellular oxidative stress. Derangement in lipid levels elevates plasma oxidized low-density lipoprotein (OxLDL) levels, which are recognized by OxLDL receptors on the membranes of neurons. This activates cellular NADPH oxidase (Nicotinamide adenine dinucleotide phosphate oxidase). NADPH oxidase generates reactive oxygen species in neurons, which elicits cellular oxidative stress [38].

Inflammatory lesions are other possible causes of the lesions. OxLDL and oxysterols are known to trigger the production of inflammatory cytokines and the expression of adhesion molecules on endothelial cells, which result in monocytes recruitment and initiation of local inflammatory lesions [39].

Ischaemia has also been suggested to be developed due to hyperlipidaemia. Stenosis of the vascular lumen and disturbed microcirculation may result owing to the hyperlipidaemic state. This lipid-induced ischemia of peripheral nerve fiber has been speculated to be involved in the development of the neuropathies [39].

Another important factor described to be linked with the hyperlipidaemic sequelae is the disturbed regulation of the lipid metabolism which along with other systematic metabolic disturbances can alter the expression levels of local adipocytokines in adipocytes distributed in many tissues [40]. Adipocytokines are found to be involved in the regulation of the lipid metabolism of the Schwann cells and neurons. Consequently, alteration of these processes leads to local dysregulation of lipid metabolism in nerves and the subsequent demyelination observed in peripheral neuropathies [39].

Conclusion

F wave study provides a reliable and sensitive electro-diagnostic measure to detect the presence of neuropathy in diabetics with F wave minimum latency, mean latency, persistence and chronodispersion as useful variables to detect the lesion. The presence of neuropathy with deranged lipid profiles and ratios in the diabetics as found in the present study provides evidence in support of the concurrence of atherogenic state with the neuropathy. This, in turn warrants investigating the diabetics with neuropathy, for their lipid profile and ratios in order to detect the macrovascular complications in pre-clinical stages.

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