ORIGINAL ARTICLE

Glycacemic Control as a Predictor of Diabetic Neuropathy

SABOOHI SAEED*, MUHAMMAD AKRAM**, QURAT-UL-AIN MAHMOOD**

ABSTRACT

Background: Distal symmetrical peripheral polyneuropathy is the most common form of neuropathy in patients of diabetes mellitus. For measurement of peripheral neuropathy, Nerve Conduction Studies (NCS) are the most non-invasive and least subjective single criterion. In diabetes due to increased glucose entry directly affect Schwann cells (or myelin) and nodes of Ranvier. In this observational study relationship present between glycaemic level and the nerve conduction velocities, among type 2 diabetic patients is found. Measurement of the sensory nerve conduction velocities of ulnar, sural nerves and motor conduction velocities of ulnar, tibial nerves was done.

Method: 42 subjects having type 2 diabetes patients with onset of disease ≤ 5 years and an age range of 40-70 years were included by simple random selection. 25 age matched healthy subjects were included as control. Nerve conduction studies were conducted in EMG room of Neurology section of Medical Unit 1 at Sir Ganga Ram Hospital, Lahore on Electromyograph by Nihon Kohden MEB-5304K. Fasting plasma glucose and glycated hemoglobin levels were estimated to find glycaemic control.

Results: The motor nerve conduction velocity of tibial nerve and sensory nerve conduction velocities of ulnar and sural nerves are highly significantly ($P<0.001$) reduced. Motor nerve conduction velocity of ulnar nerve is significantly ($P<0.05$) decreased in diabetic patients. Fasting plasma glucose and glycated hemoglobin are highly significantly ($P<0.001$) raised in the type 2 diabetics. A significant ($P<0.05$) inverse correlation of these glycaemic parameters is present with sensory ulnar, sural and motor tibial nerve conduction velocities.

Conclusion: Both glyceamic parameters including fasting plasma glucose and glycated haemoglobin exhibit inverse significant correlation with nerve conduction velocities of ulnar, tibial and sural nerves in type 2 diabetics of recent onset in age range 40-70 years. This suggests a metabolic basis for the pathogenesis of diabetic neuropathy. Hence, glycaemic parameters have been proved significant to predict the neuropathy and thus may be used in assessing other micro vascular complications of diabetes.

Key words: Diabetic neuropathy, sensory motor nerve conduction velocity, glycaemic control, fasting plasma glucose, glycated haemoglobin

INTRODUCTION

Distal symmetrical peripheral polyneuropathy is the most common form of neuropathy in patients with diabetes mellitus (Poncelet[1] 2003). Diabetic polyneuropathy once established is largely irreversible (Watkins and Thomas[2] 1998). Severe form of diabetic polyneuropathy results in significant complications including disability, morbidity, severe pain, loss of ambulation and increased risk of non healing ulcers (Poncelet 2003).

For measurement of peripheral neuropathy there is no other gold standard available except Nerve Conduction Studies (NCS) which are the most non-invasive and least subjective single criterion (Perkins[3] et al 2001). NCS include measurement of sensory and motor nerve conduction velocities of both upper and lower limbs (Potts[4] 2001).

In diabetes due to increased glucose entry and elevated cytosolic glucose in the peripheral nerves certain biochemical changes are induced (Oates and Mylari[5] 1999) that directly affect Schwann cells (or myelin) and nodes of Ranvier (Dyck and Giannini[6] 1997). So there may be a definite relationship present between glycaemic level and the decrease in nerve conduction velocities among type 2 diabetic patients (Weerasuryia[7] et al in 1998). The exact threshold of glycaemic control below which the reduction in microvacular complications is not observed and is not yet found (Stratton [8]et al 2000).

The nerve conduction velocities of two sensory and two motor nerves of upper and lower limbs are found in this study to find the extent of decrease in speed of conduction in diabetics while comparing with the control subjects.

**Physiology Department, Fatima Jinnah Medical College, Lahore.*

***Physiology Department, King Edward Medical University, Lahore*

Correspondence to Dr. Saboohi Saeed, Assistant Professor. Email: mahmoodsaboohi@ yahoo.com

Fasting plasma glucose and glycated haemoglobin were also found to assess the level of glycaemic control in these diabetics. Then correlation of these parameters is found with the decrease in conduction velocity to understand the effect of glycaemia on neuropathy quantitatively.

Method: A written consent was obtained from each subject. Nerve conduction studies were conducted in EMG room of Neurology section of Medical Unit 1 at Sir Ganga Ram Hospital, Lahore on Electromyograph by Nihon Kohden MEB-5304K. As no significant difference of conduction velocity along a nerve in right or left side of the body had been found (Joynt[9] 1989), the nerve conduction velocities in peripheral nerves of right side were studied in the ulnar nerve of upper and tibial, sural of the lower limbs. The skin temperature was maintained within 36-38 degree Celsius (Trojaborg[10] et al 1992).

Fasting plasma glucose and glycated hemoglobin levels were estimated by kits to find glycaemic control.

Subjects selection: The subjects included were type 2 diabetics having onset of disease ≤ 5 years and not having symptoms and signs of advanced micro vascular complications (Weerasuryia et al 1998).

The patients having endocrinal disorders, nerve injury, inherited neuropathy, entrapment neuropathies and cerebral stroke were not included (The Expert Committee[11] 2003).The pregnant females, chronic alcoholics and individuals having nutritional deficiency of vitamins B complexes, inflammatory diseases and advanced renal and liver diseases were ruled out in the participants by careful history and physical examination (Willison and Winer[12] 2003).

RESULTS

The experimental group included 42 type 2 diabetic patients. There were 30 females and 12 males having mean duration of diabetes 17.76 ± 19.67 months.

Table 1:Comparison of glycaemic parameters between controls and type 2 diabetics

Glycaemic Parameters	Normal controls (n=25)	Diabetics (n=42)	P value	Significance
Fasting plasma glucose (mg/dl) (FPG)	76.88 ± 13.73	162.71±40.96	P<0.001	HS*
Glycated haemoglobin (HbA1c) (%)	5.33 ± 0.48	10.12 ± 2.26	P<0.001	HS*

(mean ± standard deviation), HS* Highly significant

Table 2:Comparison of motor and sensory nerve conduction velocities between non-diabetic controls and type 2 diabetics

Nerve conduction velocity m/sec	Normal controls (n=25)	Type 2 diabetics (n=42)	P value	Significance
Ulnar (motor)	65.05±6.56	57.15±7.84	P<0.01	S*
Ulnar (sensory)	57.14±5.90	46.60±8.06	P<0.001	HS**
Tibial (motor)	63.57±11.09	44.87±10.35	P<0.001	HS**
Sural (sensory)	51.1±12.03	12.96±19.49	P<0.001	HS**

Table 3: Correlation between fasting plasma glucose (mg/dl) and sensory, motor nerve conduction velocities (m/sec) in type 2 diabetic group

Correlation between Coefficient(r)	Correlation	Regression equation	P value	Significance
FPG and MNCV (ulnar)	0.139	Y=53.75+0.02X	P>0.05	NS*
FPG and SNCV (ulnar)	-0.291	Y=55.19+-0.05X	P<0.05	S**
FPG and MNCV (tibial)	-0.357	Y=60.03 +-0.10X	P<0.05	S**
FPG and SNCV (sural)	-0.332	Y=34.49+-0.13X	P<0.05	S**

Table 4: Correlation between glycated haemoglobin (%) and sensory, motor nerve conduction velocities (m/sec) in type 2 diabetic group

Correlation between Coefficient(r)	Correlation	Regression equation	P value	Significance
HbA_1c and MNCV (ulnar)	-0.125	Y=53.36+0.41X	P>0.05	NS*
HbA_1c and SNCV (ulnar)	-0.493	Y=64.36+-1.75X	P<0.05	S**
HbA_1c and MNCV (tibial)	-0.419	Y=67.24+-2.35X	P<0.05	S**
HbA_1c and SNCV(sural)	-0.092	Y=19.95+-0.74X	P>0.05	NS*

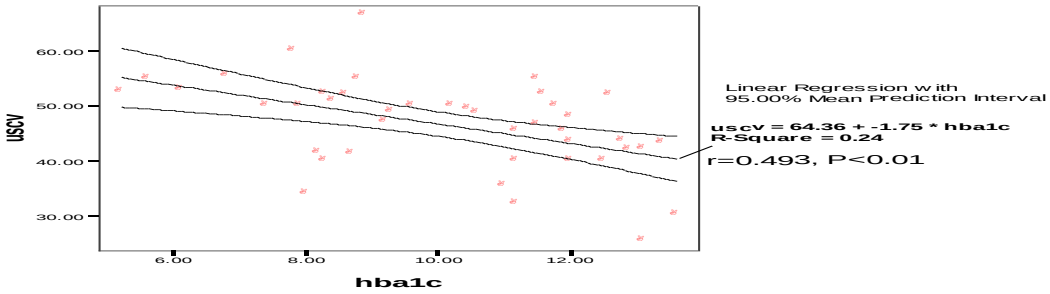
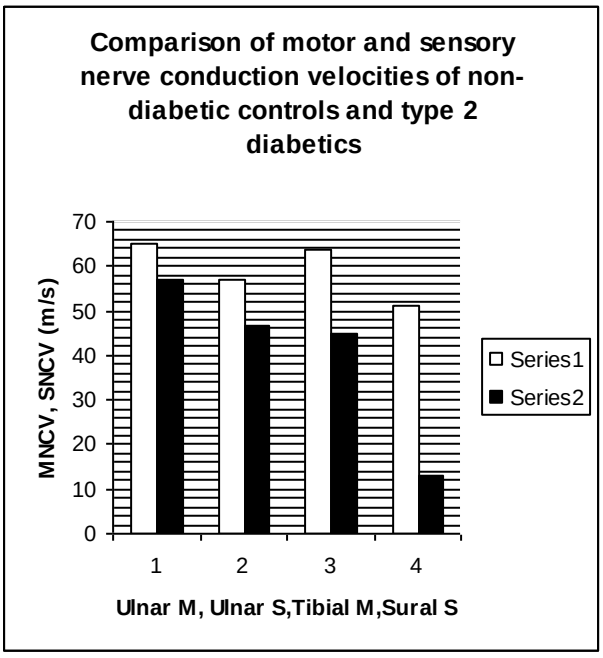


Figure 2: Graph showing correlation between glycated hemoglobin (%) and ulnar sensory nerve conduction velocity . (The line represents the regression li r= Correlation coefficient)



MNCV Motor nerve conduction velocity
SNCV Sensory nerve conduction velocity
M=Motor, S=Sensory

DISCUSSION

Both glycaemic indices showed significantly higher (P<0.001) values (Mean ±SD) including fasting plasma glucose 162.71±40.96 mg/dl and glycated haemoglobin 10.12 ± 2.26 % in type 2 diabetics versus 76.88 ± 13.73 mg/dl and 5.33 ± 0.48 % in age matched healthy controls respectively. Fasting plasma glucose level denotes the present glycaemic control. Glycated haemoglobin (HbA_1c) is the quantitative index of average glycaemia 6-10 weeks before (Borsey[13] et al 1982).

The results of peripheral nerve conduction velocities revealed that mean motor nerve conduction velocities (MNCV) of ulnar and tibial nerves, and mean sensory nerve conduction velocities (SNCV) of the ulnar and sural nerves were significantly (P<0.001) reduced among type 2 diabetics with recent onset. This is in accordance with the dominant histopathological finding in diabetic neuropathy that is segmental demyelination (Herrman[14] et al 2002). This result in loss of large, fast conducting fibers and slowing down of nerve conduction velocities (Bae[15] et al 2007).

It was found that nerves of the lower limb were more intensely affected than the nerves in the arms. This may be on account of greater nerve length in the lower limb. So, peripheral neuropathy seems to be a length dependent phenomenon affecting first the most distal parts of the peripheral nerves (Willison and Winer 2003).

This study indicated further that peripheral nerve disturbances were more common in the sensory nerves than in the motor nerves. So the sensory nerves are more susceptible to damage than motor nerves as these lack thick myelin sheath (Graf[16] et al 1981).

A statistically significant inverse correlation was manifested by the glycaemic parameters including fasting blood glucose and glycated haemoglobin levels, with the motor and sensory nerve conduction velocities of all the nerves studied in recent onset type 2 diabetics. The nerve conduction velocity in the peripheral nerves decreased significantly with increase in the fasting plasma glucose and glycated haemoglobin levels in type 2 diabetic patients.

Fasting plasma glucose level shows inverse significant correlation (P<0.05) with sensory conduction velocities of ulnar (r=-0.365), sural (r=-0.366) nerves and motor conduction velocity of tibial (-0.540) nerve in recently diagnosed diabetics. Glycated haemoglobin as well holds a highly significant inverse relation (P<0.01) with both sensory (ulnar nerve=-0.493) and motor (tibial nerve=-0.454) nerve conduction velocities.

The significant correlations between glycaemic parameters and peripheral nerve conduction velocities suggests that hyperglycaemia induced metabolic disturbances play a vital role in the pathogenesis of peripheral diabetic neuropathy. A definite and precise relation exists between the extent of hyperglycaemia and degree of fall in the speed of nerve conduction, as indicated by regression analysis in this study that for each one percent rise in glycated haemoglobin there is 1.75 meter/second fall in sensory conduction velocity of ulnar nerve and 2.35 meter/second decrease in motor conduction velocity of tibial nerve.

Measurement of both of these glycaemic parameters simultaneously in a diabetic patient provides a detailed profile of previous and recent glycaemic control. So the record of the glycaemic profile during a specified period can help the physician to predict the degree of nerve damage and to determine the extent of effective glycaemic control essential for such patient to prevent further progression of neuropathy as currently the optimizing of glycaemic control is the only remedy available (Diabetes Control and Complications Trial Research Group[17] 1993).

CONCLUSION

1. Nerve conduction velocities have been significantly decreased in sensory as well as motor peripheral nerves among type 2 diabetics of recent onset in both upper and lower limbs. Thus this test must be employed earlier to diagnose neuropathy.
2. A highly significant negative correlation between velocity of nerve conduction and glycaemic control suggests a metabolic basis for pathogenesis of diabetic neuropathy. Hence, both glycaemic parameters fasting plasma glucose and glycated hemoglobin have been proved significant to predict the onset and progression of neuropathy and may be used in assessing other micro vascular complications of diabetes.
3. Moreover, the patients must be educated about maintaining strict glycaemic control to avoid the disability and morbidity of progressive neuropathy.

REFERENCES

1. Poncelet Ann Noelle. Diabetic neuropathy and foot ulcer. Risk factors, patterns of presentation, diagnosis and treatment. Geriatrics 2003; 58; 6: 16-30.
2. Watkins PJ and Thomas PK. Diabetes mellitus and the nervous system J Neurol Neurosurg Psychiatry 1998; 65: 620-632.
3. Potts Frisso A. Approach to the patient with peripheral neuropathy. Best Practice of Medicine 2001, 337.
4. Perkins Bruce A, Greene DA and Bril Vera. Glycaemic control is related to the morphological severity of diabetic sensorimotor polyneuropathy. Diabetes Care 2001; 24: 748-752.
5. Oates PJ and Mylari BL. Aldose reductase inhibitors. Therapeutic implications for diabetic complications. Expert Opin Investig. Drugs 1999; 8; 12: 2095-2119.
6. Dyck PJ and Giannini C. Pathological alterations in the diabetic neuropathies of humans: a review J Neuropathol Exp. Neurol 1997; 56; 4: 458.
7. Weerasuriya N, Siribaddana S, Wijeweera I, Dissanayeka A, Wijesekera J and Fernando DJS. The prevalence of peripheral neuropathy in newly diagnosed patients with non-insulin dependent diabetes mellitus. Ceylon Medical Journal 1998; 43: 19-21.
8. Stratton Irene M, Adler AI, W Neil H Andrew, Mathews David R, Turner RC, Manley SE, Cull CA, Hadden D and Holman R R. Association of glycaemia with macro vascular and micro vascular complications of type 2 diabetes (UKPDS 35). BMJ 2000; 321; 405-412.
9. Joynt RL. Correlation studies of velocity, amplitude and duration in median nerves. Arch Phys Med Rehabil 1989, 70: 477-481
10. Trojaborg Werner T, Moon Agnes, Andersen Birgitte B and Trojaborg Nanna S. Sural nerve conduction parameters in normal subjects related to age, gender, temperature and height: a reappraisal. Muscle and Nerve 1992; 15: 666-671.
11. The Expert Committee on the diagnosis and classification of Diabetes Mellitus. “Report of the Expert Committee on the Diagnosis and Classification of Diabetes Mellitus.” American Diabetes Association 2003; Diabetes Care 2003; 26 : S5-S20
12. Willson J Hugh and Winer John B. Clinical evaluation and investigation of neuropathy. Journal of Neurol Neurosurg Psychiatry 2003; suppl ii: ii3-ii8
13. Borsey DQ, Fraser DM, Gray RS, Elton RA, Smith AF. Glycosylated haemoglobin and its temporal relation to plasma glucose in non insulin dependent type 2 diabetes mellitus. Metabolism 1982; 31: 362-365.
14. Herrmann DN, Ferguson ML, Logigian EL. Conduction slowing in diabetic distal polyneuropathy. Muscle and Nerve 2002; 26 2: 232-237.
15. Bae Jong Seok, Park Sung Sik, Kim Minky and Kim Byoung Joon. Conduction slowing in painful versus painless diabetic neuropathy. Journal of Clinical Neuroscience; 2007; 14; 1: 22-26
16. Graf Ronald J, Halter Jeffery B, Pfeifer Michael A, Halar Eugen, Brozovich Frank and Porte Daniel. Glycaemic control and nerve conduction abnormalities in non insulin dependent diabetic subjects. Annals of Internal Medicine 1981; 94; 3:307-311
17. Diabetes Control and Complications Trial Research group. The effect of intensive treatment of diabetes on the development and progression of long term complications in insulin dependent diabetes mellitus. The England Journal of Medicine 1993; 329; 14: 977-986