www.jmscr.igmpublication.org
Impact Factor 5.84
Index Copernicus Value: 71.58
ISSN (e)-2347-176x ISSN (p) 2455-0450
crossref DOI: https://dx.doi.org/10.18535/jmscr/v5i10.57

IGM Publication
Journal Of Medical Science And Clinical Research
An Official Publication Of IGM Publication

Investigating the use of biothesiometer for Detecting the Severity of Diabetic Neuropathy in Diabetic Type- II Patients

Authors
Dr M Madhavi Latha[1], Dr Susmitha Yella[2]
[1]Department of Physiology, NRI Medical College
[2]Department of Neurology, NRI Medical College
Corresponding Author
Dr Susmitha Yella
Department of Neurology, NRI Medical College

Abstract
Diabetes Mellitus is a double edged sword which can result in both microvascular and macrovascular complications, of which Diabetic Neuropathy has been reportedly under diagnosedor misdiagnosed. With changing technologies different methods of diagnosis have come to light for the diagnosis of Diabetic Neuropathy, of which Diabetic neuropathy symptom score by Dyck and measurement of vibration Perception Threshold by Biothesiometer were compared in this study to investigate any correlation between the methods. In this study, Diabetic neuropathy symptom score by Dyck is measured by the symptoms experienced by the subjects and relevant score is given whereas on the other hand, the VPT (Vibration Perception Threshold) value is measured using a Biothesiometer and the voltages measured were recorded. Extensive statistical analysis were performed involving chi-square correlation (for categorical relationship), linear regression (for continuous variables) and multivariate analysis to deduce dependence of outcomes on the various parameters like age, BMI, duration of disease and the diabetes control measured as Hb1Ac values. The results concluded that, the diagnosis of diabetic neuropathy by biothesiometer has been reliable to be compared with diabetic neuropathy symptom score and can aid in the earlier detection of the disease.
Keywords: *Diabetes mellitus, Diabetic neuropathy, Diabetic neuropathy symptom score, VPT, Biothesiometer.*

Introduction

Diabetes mellitus is a group of disorders of fat, carbohydrate and protein metabolism which results in defects from insulin secretion, insulin action or both. In 2016, epidemiological studies show a dramatic rise of diabetes mellitus in India from 11.9 million in 1980 to 64.5 millions. Where the prevalence of diabetes mellitus has more than doubled for men (3.7%-9%) and also increased by 80% among women in India [1,2].

Due to inconsistent hyperglycemia, a number of abnormalities appear to cascade into a viscous cycle of progressive microvascular disease associated with motor, sensory and autonomic fibre loss, resulting in the condition known as "Diabetic Neuropathy" [3].

Diabetic neuropathy being the regular complication seen in type 2 diabetes mellitus characterized by the paresthesia, numbness or pain as predominant symptoms. The prevalence of diabetic neuropathy is estimated at approximately 30-40% and even up to 50% as the duration of diabetes increases[4]. Early detection of Diabetic neuropathy (DNP) is important in patients with diabetes as preventive measures can be applied to decrease morbidity.

Diagnostic test for diabetic neuropathy desired to be reliable, affordable and easily available. There are many accepted examination scores for diabetic neuropathy which includes Neuropathy Disability Score (NDS), neuropathy symptom score by DYCK, Neuropathy Impairment score in the lower limbs (NIS-LL) and various modified NDS scores[5]. For diagnosis of the diseases at least the use of two of the following approaches are recommended, viz., signs, symptoms, quantitative sensory testing, nerve conduction study and autonomic testing[6]. The neurological examination in outpatient setting which is the component of the diagnostic investigation of the neuropathy should be highly sensitive, simple and fast and shouldn't require expensive specialist equipment. In clinical situations the gold standard for diagnosis of diabetic neuropathy are nerve conduction studies however they are expensive and are time consuming procedures. Considering the economic aspect, ease of accessibility and accuracy, we have decided to choose Biothesiometer as a quantitative approach which involves measurement of Vibration Perception Threshold (VPT) by applying certain voltage at the distal plantar surface of great toe of both the legs and recording the first felt vibration sense. The means of 3 records are taken and neuropathy diagnosed if VPT greater than or equal tocertain fixed value [7-9]. In the current study we attempted to build a relationship between biothesiometer VPT readings and the clinical diabetic neuropathy based on the patient reported signs and symptoms following a simple 4 stages classification of the disease. Also, the influence of factors like age of the patients, duration of the diabetes and how the diabetes was maintained was determined for both biothesio-meter readings and the stages of the clinical diabetic neuropathy.

Materials and Methods

A prospective, cross-sectional study was performed on the diabetic type-II (T2DM) patients visiting the Neurology & Diabetology departments of NRI Medical College, (address). Inclusion criteria for the study were, age Age ≥30 years with T2DM and the duration of diabetes >_1 year at the time of presentation. And the exclusion criteria for the study were, patients with insulin dependent diabetes, has severe ulceration of feet, reported history of alcoholism and smoking, patients with known renal, cardiac, pulmonary or hepatic diseases and patients with history of nerve compression & other known causes of neuropathy. A total of 57 patients including males and females, who met both inclusion and the exclusion criteria were recruited into the study. Patients were explained about the experimental procedure in detail, signed the informed consent forms and anthropometric readings were taken. Height (meters) and weight (kilograms) were measured and body mass index (Kg/m_2) was calculated. Blood pressure (mmHg) was recorded. A blood sample was collected to measure fasting blood sugar, glycated haemoglobin (HbA1c) to indicate the glycemic status of the subjects.

Diabetic neuropathy symptom (DNS) score

Patients were asked for any symptoms they had and their answers were allotted points according to the Neuropathy Symptom Score (NSS) recommended by Dyck et al[10]. If answer is 'yes' for a symptom occurring more times per week during the last 2 weeks, then 1 point is allotted per each symptom. If it is 'no', then no points are given. The symptoms were,

1) Unsteadiness in walking
2) Burning, aching pain or tenderness in the legs or feet
3) Pricking sensations in the legs and feet

4) Numbness on the legs or feet

A score of 0 implies absent of clinical diabetic neuropathy (DN), 1 implicates mild DN, 2 Moderate DN, 3 advance DN and a score of 4 implicates severe DN.

Vibration perception threshold (VPT) was measured with a Biothesiometer: Measurements were recorded by a single observer who was blinded to the clinical evaluation for DN. The Biothesiometer probe, vibrating at an amplitude proportional to the square of the applied voltage, was applied perpendicular to the test site with a constant and firm pressure. VPT was then measured at the distal plantar surface of great toe of both the legs. The voltage was slowly increased at the rate of 1 mV/sec and the VPT value was defined as the voltage level when the subject indicated that he or she first felt the vibration sense. The mean of three records wastaken.

Statistical analysis

Primary aim of the study is to find a relation between the DN status of the diabetic patients based on the DNS scores and biothesiometer readings for the respective patient. To accomplish this two statistical tests were performed using SPSS software (Version 22, SPSS, Chicago, Illinois, USA), 1.A linear regression test to investigate any relation between the biothesiometer readings, transformed for normality as reported by Gary et al[11], as recorded from the equipment as a continuous variable and by transforming the ordinal variable of DNS score into a dummy variable with mild category as comparing level with other levels. For linear regression mean value for the biothesiometer readings for each level of the DNS scores were calculated from the SPSS output using regression equation "y=bx+c", were y is the mean of interest, b is SPSS generated unstandardized coefficient value for respective score and c is the constant from the analysis, for difference between in the mean in comparison to mild level was considered significant if $p<0.05$. 2. A chi-square test by using biothesiometric determined diabetic neuropathic status (BNPS) as a nominal variable with three levels viz., BNPS-1 (biothesiometer reading of < 15); BNPS-2 (for biothesiometer reading of 15 to 25.00) and BNPS-3 (for biothesiometer reading of > 25) based on the 95% confidence interval values for biothesiometer readings obtained from the linear regression analysis, chi-square test Z values were calculated from the post-hoc analysis of the Chi-square test and significance value, "p" was computed as described by Beasley et al, 1995 [12]. Results of the analysis were considered significant if *p value* was less than "0.0042" following bonferroni correction for 4*3 cross tabulation comparisons (0.05/12).

Secondary aim was to deduce dependence of various variables on the BNPS and DNS scores. For this two independent Multivariate analysis of variance were performed using SPSS software (Version 22, SPSS, Chicago, Illinois, USA). Age of the patient, duration of diabetes, BMI, and HbIAc were taken as dependent variables in both the analyses and were transformed for normality as reported by Gary et al[11]. Stages of the patients being detected as diabetic neuropathic by biothesiometer (3 levels) and DNS score (4 levels) reflecting the symptoms of diabetic neuropathy were taken as factors for respective analysis. Differences in the BM readings from the left and the right were found be statistically not significant (t-test, $p>0.7$ at $\alpha=0.05$), as such average of the readings used to further categorize the patients into BNPS-1, BNPS-2 and BNPS-3. Assumption to multivariate analysis including no missing data, outliers, normality for dependent variables, homogeneity of variance and homogeneity of regression slopes were all met. A subject who was the only one to score "zero" on the DSN score was excluded from the study.

Results

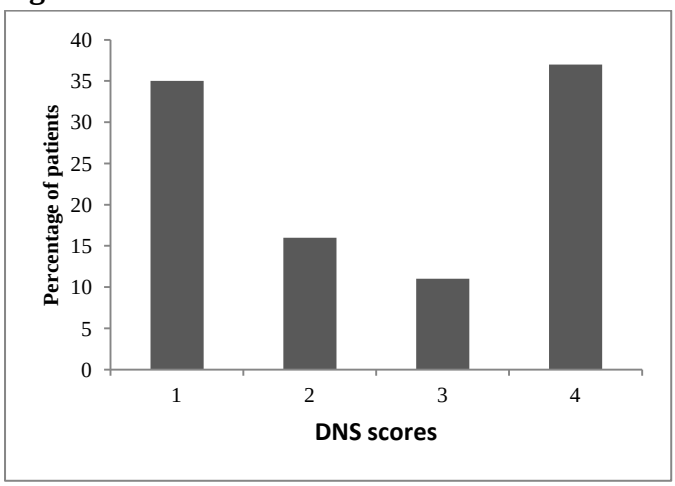
Total of 57 patients were recruited for the study which included 30 males and 27 females. Mean age of the patients was 54 years, mean duration of the diabetes was 5.8 years, mean BMI was 28.5 and mean Hb1Ac was 7.3, table 1. Based on the

DNS scores, 20(35%) patients showed mild diabetic neuropathy symptoms followed by 9 (16%) with moderate, 6 (11%) with advance and 21 (37%) with severe diabetic neuropathy symptoms, figure 1.

Table 1: Demographics of the diabetic type-II patients included in the study.

Parameter	Mean and range
N	57
Age (years)	54.1 (27- 71)
Gender (M/F)	30/27
Duration of diabetes (years)	5.8 (1.2 -12)
BMI	28.5 (24-33)
Hb1Ac	7.3 (6-9.1)

Fig 1



Linear regression analysis between Biothesiometer reading and the DNS scores

There was a good correlation between the DNS scores and the biothesiometer readings with a correlation efficient of "0.861" accounting for about 74% (R2= 0.74) of differences explained by the biothesiometer readings. Mean values for biothesiometer readings for patients with moderate, advance and severe DNS scores were significantly higher compared to the patients with mild DNS score. Table 2, summaries the results from linear regression analysis. Based on these results, biothesiometer readings were classified into three categories, BNPS-1, BNPS-2 and BNPS-3, to match with the DNS scores based on the 95% confidence intervals (table 2). BNPS-1 for none or mild neuropathy corresponding to the biothesiometer reading of less than 15. BNPS-2 for moderate or advance neuropathy corresponding to the biothesiometer reading between 15 and 25 correlated with the combined DNS scores corresponding to moderate and advance DNS scores as there was an overlap in their 95% CI (table 2) and also there no statistical significant difference noted between the groups (results not presented). BNPS-3 for biothesiomter readings of more than 25 to suggest severe neuropathy.

Chi-square test of independence between BNPS and DNS scores

The chi-square test showed a significant relationship between BNPS and the DNS score, $X2$ (6, N = 56) = 47.00, $p < 0.001$. Further post hoc analysis gave a significant correlation between BNPS and DNS score of mild, moderate, and severe with biothesiometer determined status of BNPS-1, BNPS-2 and BNPS-3 respectively ($P<0.0042$ for all). However, there was no significant relation for the patients whose DNS score is advance with any of the neuropathy status determined by the biothesiometer. Table 3, is the crosstabulation generated by SPSS for biothesiometer reading and DNS scores. Also there was a significant negative correlation for BNPS-1 status and the severe DNS score and for BNPS-3 and mild DNS score, suggesting BNPS is immune to give false positive and false negative outcomes.

Table 2:

DNS score	Biothesiometer readings	
	Mean	95% confidence interval
Mild	13.26	11.68 – 14. 85
Moderate	19.65*	16.80 - 22.50
Advance	21.84*	18.53 - 25.14
Severe	26.69*	24.46 - 28.91

*-Statistically significant difference compared to individuals with mild DNS score ($p< 0.001$)

Table 3: SPSS generated 4*3 crosstabulation for Biothesiometer neuropathy status (BNPS) vs DNS scores

			BNPS			Total
			BNPS-1	BNPS- 2	BNPS-3	
DNS scores	Mild	Count	13*	7	0#	20
		% within DNS scores	65.0%	35.0%	0.0%	100.0%
	Moderate	Count	0	9*	0	9
		% within DNS scores	0.0%	100.0%	0.0%	100.0%
	Advanced	Count	0	5	1	6
		% within DNS scores	0.0%	83.3%	16.7%	100.0%
	Severe	Count	0#	9	12*	21
		% within DNS scores	0.0%	42.9%	57.1%	100.0%
Total		Count	13	30	13	56
		% within DNS scores	23.2%	53.6%	23.2%	100.0%

*- Significant positive correlation #- Significant negative correlation.

MANOVA

Dependable variables on BNPS

MANOVA model for BNPS detected a significant main effect of all dependable variables with Pillai's trace= 0.740, F (8,102) = 7.494, p< 0.001, size effect= 0.370. The main effect of variables, age, duration as a diabetic, BMI and Hb1Ac was significant over BNPS with statistics: age- F(2,53)= 4.836, p=0.012, size effect= 0.154; duration as diabetic- F(2,53)= 7.720, p= 0.001, size effect= 0.226; BMI- F(2,53)= 4.038, p= 0.023, size effect= 0.132; Hb1Ac- F(2,53)= 18.434, p< 0.001, size effect= 0.410. Mean age differences between BNPS-1 and BNPS-3 (9.8 years older) and for BNPS-2 and BNPS-3 (6.8 years older) were sufficiently different (p<0.05), table 3. LSD post hoc analysis comparisons for age, duration of disease, BMI and Hb1Ac are significantly different for different categories of BNPS: Age for BNPS-1 & BNPS-2, BNPS-2 & BNPS-3 and BNPS-2 & BNPS-3; DMT for BNPS-1 & BNPS-2, BNPS-1 & BNPS-3; BMI for BNPS-1 & BNPS-2; Hb1AC for BNPS-1 & BNPS-3 and BNPS-2 & BNPS-3.

Table 3:

	BNPS	Mean	Std. Deviation	N
AGE*	BNPS-1	50.75	8.21	13
	BNPS- 2	53.72	8.33	30
	BNPS-3	60.60	8.78	13
	Total	54.63	8.97	56
DMT*	BNPS-1	4.24	1.95	13
	BNPS- 2	6.13	2.10	30
	BNPS-3	7.23	1.68	13
	Total	5.94	2.20	56
BMI*	BNPS-1	30.06	2.15	13
	BNPS- 2	27.83	2.34	30
	BNPS-3	28.71	2.67	13
	Total	28.55	2.51	56
Hb1Ac*	BNPS-1	6.77	.69	13
	BNPS- 2	7.13	.65	30
	BNPS-3	8.15	.38	13
	Total	7.29	.78	56

*- statistically significant.

Dependable variables on DNS score

MANOVA model for DNS scores detected significant main effect of all the dependable variables, with Pillai's trace= 0.880, F (12,153.0)= 5.296, p<0.05, p< 0.001, size effect= 0.293. The main effect of variables, age, duration as a diabetic and Hb1Ac was significant over DNS scores with statistics: age- F(3,52)= 3.180, p=0.031, size effect= 0.155; duration as diabetic- F(3,52)= 11.992, p< 0.001, size effect= 0.409;

Hb1Ac- F(3,52)= 16.580, p< 0.001, size effect= 0.489. LSD post hoc analysis comparisons indicate there is a significant difference in age, duration as a diabetic and Hb1Ac for between subjects who were scored mild and severe for DNS (P<0.05 for all). Table 4:

Table 4:

	DNS scores	Mean	Std. Deviation	N
AGE*	Mild	50.47	8.38	20
	Moderate	53.41	9.93	9
	Advanced	57.71	7.78	6
	Severe	58.22	8.12	21
DMT*	Mild	4.29	1.84	20
	Moderate	5.95	2.08	9
	Advanced	5.82	.80	6
	Severe	7.55	1.67	21
BMI	Mild	29.07	2.48	20
	Moderate	27.08	2.33	9
	Advanced	27.62	2.54	6
	Severe	28.95	2.44	21
Hb1Ac *	Mild	6.83	.65	20
	Moderate	6.70	.49	9
	Advanced	7.33	.36	6
	Severe	7.95	.57	21

*- statistically significant.

Discussion

This study for the first time attempted to build a relation between the biothesiometer readings and severity of the clinical neuropathy in diabetic patients by correlating with the symptoms based DNS scores of the disease. Earlier studies in this arena mostly were focused on the use of biothesiometer to detect the presence or absence of neuropathy in diabetic patients. In this study, we successfully able to demonstrate that biothesiometer readings can further be classified into 3 ordinal categories to imply the severity of the diabetic neuropathy in the patients.

Biothesiometer as an equipment to aid in the detection of DN has been in practice for more than 5 decades and is still an economical alternative to detect DN in diabetic patients. DNS scores suggested in this study is a simple 4 level determination of the severity of the disease ranging from mild, moderate, advanced and severe. Current study incorporated various methods to analyse the results, linear regression analysis was used to get the 95% confidence intervals for the biothesiometer readings which fall in the categories of clinical severity of DN. Except for the mild DN, for other categories of DN there was no clear distinction, especially for moderate and advance clinical DN, as such biothesiometer readings were classified into 3 categories to match with the clinical DN. Further Chi-square correlation showed a significant correlation between the mild clinical DN and BNPS-1; moderate clinical DN and BNPS-2; and advanced clinical DN and BNPS-3. As such results from this study suggest biothesiometer can be used to categorise DN into three categories based on the measurements obtained.

These results needs to be interpreted with caution as this study lacks the patients with no DN to sever as controls. Such a comparison can be achieved in larger patient groups to get a precise cut off values for biothesiometer readings to distinguish the severity of diabetic neuropathy and perhaps can assist in the early detection of the disease progression. In the current study all the patients showed some degree of DN with exception to only one patient with no symptoms of DN who was excluded from the analysis as being only one in the category. Future studies with the inclusion of newly diagnosed patients who are less likely to develop DN can serve as controls for the study. However, this study provided a good correlation between the biothesiometer readings and the clinical DN status of diabetic patients ranging from mild to severe symptoms and hence can be used for patients who used some or other symptoms for DNP.

Results from this study were consistency with the previous reports in terms of the relation between the age of the patient, duration of diabetes and the poor control of the disease with both clinical DN and biothesiometer readings. All these factors found to contribute to the severity of DN.

However, we were not able to find a relation between the BMI of the individual and the severity to DNP perhaps most the patients included in the study were aged and difference in their BMI were profound, table 4. Future studies with the inclusion patients with different BMI can perhaps provide a better correlation in BMI and the DNP status specifically in Indian populations as reported studies are sparse.

Conclusion

Biothesiometer readings well correlated with clinical DN severity. Based on biothesiometer measurements patients can be categorised into three categories ranging from mild to severe DN. As such this study validates in house use of the device to aid in early detection of DNP in diabetic patients. However, for wide spread use in all clinical settings, further confirmative studies are warranted involving diverse patients in terms of duration of the disease, BMI and DNP status ranging from non to severe.

Acknowledgments

We extend our thanks to Scribefast (www.scribe-fast.com) for editing/proof reading services and Dr. Mohi Iqbal Mohammed Abdul, Taibah University, Saudi Arabia for assisting in statistical analysis for the study.

Author contributions: Disclosure

References

1. International Diabetes Federation. IDF Diabetic Atlas 7th Edition. http://www.idf.org/idf-diabetes-atlas-seventh-edition. Accessed 30 Aug 2017.
2. Kaveeshwar SA, Cornwall J. The current state of diabetes mellitus in India. Australas Med J 2014;7(1):45-8.
3. Morsi M, Maher A, Metwally A, Abo-Elmagd O, Johar D, Bernstein L. A Shared Comparison of Diabetes Mellitus and Neurodegenerative Disorders. J Cell Biochem 2017.
4. Deshpande AD, Harris-Hayes M, Schootman M. Epidemiology of diabetes and diabetes-related complications. Phys Ther 2008;88(11):1254-64.
5. Yang Z, Chen R, Zhang Y, Huang Y, Hong T, Sun F, et al. Scoring systems to screen for diabetic peripheral neuropathy. Cochrane Database of Systematic Reviews 2014(3).
6. Bansal V, Kalita J, Misra UK. Diabetic neuropathy. Postgrad Med J 2006;82(964): 95-100.
7. Young MJ, Breddy JL, Veves A, Boulton AJ. The prediction of diabetic neuropathic foot ulceration using vibration perception thresholds. A prospective study. Diabetes Care 1994;17(6):557-60.
8. Saha D, Saha K, Dasgupta PK. Vibration sense impairment in diabetes mellitus. Indian J Physiol Pharmacol 2011;55(4): 381-3.
9. Ogbera AO, Adeleye O, Solagberu B, Azenabor A. Screening for peripheral neuropathy and peripheral arterial disease in persons with diabetes mellitus in a Nigerian University Teaching Hospital. BMC Res Notes 2015;8:533.
10. Dyck PJ, Davies JL, Litchy WJ, O'Brien PC. Longitudinal assessment of diabetic polyneuropathy using a composite score in the Rochester Diabetic Neuropathy Study cohort. Neurology 1997;49(1):229-39.
11. Templeton GF. A Two-Step Approach for Transforming Continuous Variables to Normal: Implications and Recommendations for IS Research. Communications of the Association for Information Systems 2011;28(Article 4).
12. Beasley TM, Schumacker RE. Multiple Regression Approach to Analyzing Cont-ingency Tables: Post Hoc and Planned Comparison Procedures. The Journal of Experimental Education 1995;64(1):79-93.