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Predictive Model of Diabetic Polyneuropathy Severity Based on Vitamin D Level

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Abstract

BACKGROUND: Type 2 Diabetes Mellitus is one of the most common metabolic diseases worldwide. The most common complication of DM is diabetic neuropathy (DN), especially diabetic polyneuropathy (DPN). Vitamin D plays an important role in the pathogenesis of DN, thus affecting its severity which can be assessed using nerve conduction study (NCS).

AIM: This study aimed to develop a predictive model of DPN severity based on vitamin D level.

METHODS: This was a prospective cohort study involving 50 subjects with DM which was conducted in Haji Adam Malik General Hospital Medan. All subjects were fulfilling inclusion criteria underwent laboratory examination to determine HbA1c and 25 (OH) D levels. Predictive variables were sex, age, duration of DM, smoking status, type and number of anti-diabetic drugs, the presence of metabolic syndrome, HbA1c and vitamin D levels. A scoring system was developed to determine a predictive model. The DPN severity was assessed using NCS and was re-evaluated after 3 months.

RESULTS: Most of the subjects were female (60%), belonged to ≥ 50 years old age-group (88%), with DM duration < 5 years (56%), were non-smoker (90%), we're using one anti-diabetic drug (60%), were using insulin (50%), had metabolic syndrome (68%), had HbA1c level > 6.5% (94%), and had vitamin D level < 20 ng/ml (56%). A score of > 4 on this predictive model of DPN severity had a relative risk (RR) of 2.70. The predictive model had a sensitivity of 82.8% and specificity of 61.9%.

CONCLUSION: A score of higher than 4 on this predictive model showed a 2.7 times higher risk of severe DPN. A predictive model of DPN severity based on vitamin D level had high sensitivity and specificity.

Introduction

Diabetic neuropathy (DN) is the most common complication of diabetes mellitus (DM) [1], [2]. Its prevalence is high in developed countries. It is related to greater mortality, morbidity and higher economic burden and rate of hospitalisations [3], [4]. Chronic diabetic polyneuropathy (DPN) is the most common type of DN, accounting for about 75% of DN [5], [6]. American Diabetic Association recommends that all diabetic patients should be screened for DN at the time of diagnosis in type 2 DM and five years after diagnosis of type 1 DM [3], [7]. Once established, neuropathy is difficult to reverse [4]. Neurological examinations and careful evaluation of neuropathic signs and symptoms are important in early detection and severity determination [8]. Nerve conduction study (NCS) can detect neural changes even before the sign develops and determine the severity of neuropathy [9].

Vitamin D may have a direct effect on the pathogenesis of DN, particularly vitamin D_3 that has been shown the ability to reduce demyelination in an experimental model [10]. Serum 25-hydroxyvitamin D (25 (OH) D) is the major circulating form of vitamin D. Some studies showed vitamin 25 (OH) D deficiency is associated with DPN [11], [12]. In Asian, diabetic patients with vitamin D deficiency are 1.22 times more likely to suffer from DPN compared with those with normal vitamin D level [13].

The aim of this study was mainly to develop a predictive model of DPN severity based on vitamin D level, that can be clinically used for early detection, severity prevention of DPN so the treatment can be

optimised and may improve the quality of life of type 2 DM patients.

Material and Methods

This was a prospective cohort study which was conducted in Haji Adam Malik General Hospital Medan and had been approved by the Local Ethical Committee. Inclusion criteria were typed 2 DM patients with DPN. Exclusion criteria were patients with impaired renal or hepar function, consumption of anti-tuberculous drugs or chemotherapy. All subjects signed an informed consent before the examination. We recorded data from the subjects such as sex, age, duration of DM, smoking status, type and number of anti-diabetic drugs, and the presence of the metabolic syndrome. All subjects underwent NCS examination by the same neurologist using Cadwell ENMG (electroneuromyography) machine. HbA1c level was evaluated using the enzyme immunoassay method, and serum vitamin 25 (OH) D status was evaluated using the chemiluminescent immunoassay method. The NCS was repeated after 3 months to assess DPN severity.

The predictive variables consisted of demographic and clinical data, combined with HbA1c and vitamin 25(OH)D levels. Results of NCS after 3 months were classified using Baba's Diabetic Neuropathy Classification (BDC), consisted of BDC-0: no NCS abnormalities, BDC-1: delay in any MCV, SCV, BDC-2: sural amplitude < 5 μV, BDC-3: plantar muscle-CMAP amplitude to 2 – 5 mV, BDC-4: plantar muscle-CMAP < 2 mV.[14] We classified BDC-1 was mild and BDC-2 – 4 was severe. A scoring system was developed; the total value was 0 – 12.

The predictive variables were categorical data. The predictive variables as independent variables and DPN severity as a dependent variable. The association of predictive factors and score with DPN severity was assessed using a Chi-Square Test or Fisher's Test. The results were considered significant at $p < 0.05$. Risk Ratio (RR) for each group was calculated. The statistical calculations were done using the computerized program.

Results

There were 50 patients included in this study. Age, sex, ethnicity, duration of diabetes and glycemic control are established risk factor for DN [15]. High body mass index, hypertension and smoking are established risk factors for DN [16]. Age, an insulin treatment, longer duration of DM, and higher HbA1c were independently significant risk factors for DPN [17]. Metabolic syndrome, including pre-diabetes, are potential risk factors for neuropathy [18], [19]. Skalli et al. 's study (2012) found diabetic neuropathy was significantly linked to age, diabetes duration, and vitamin D status [12].

Based on previous studies, we selected some risk factors to be the predictive factors. The predictive factors consisted of sex, age, duration of DM, smoking status, type and number of anti-diabetic drugs, the presence of metabolic syndrome, HbA1c and vitamin 25(OH)D levels. A scoring system is shown in Table 1.

Table 1: The Predictive Score

Characteristics	Parameters	Score
Sex	Male	0
	Female	1
Age group (years)	< 50	0
	≥ 50	1
Duration of DM (years)	< 5	0
	≥ 5	1
Smoking status	No	0
	Yes	1
Number of anti-diabetics	1	0
	> 1	1
Type of anti-diabetic	Insulin	0
	Oral	1
	Combination	2
Metabolic syndrome	No	0
	Yes	1
HbA1c levels (%)	< 6.5	0
	≥ 6.5	1
Vitamin 25 (OH) D levels	≥ 30	0
(ng/ml)	20–29.9	1
	10–19.9	2
	< 10	3
Total		0 – 12

As shown in Table 2, most of the subjects were female (30 subjects, 60%), 44 subjects (88%) belonged to ≥ 50 years old age-group, 28 subjects (56%) with DM duration < 5 years, 45 subjects (90%) were non-smoker, 30 subjects (60%) were using one anti-diabetic drug, 25 subjects (50%) were using insulin, 34 subjects (68%) had metabolic syndrome, 47 subjects (94%) had HbA1c level ≥ 6,5%, and 28 subjects (56%) had vitamin 25(OH)D level < 20 ng/ml.

Table 2: Association of Predictive Factors with DPN Severity

Predictive Factors	DPN severity		p	RR	95% CI
	Mild	Severe			
Sex			0.349[a]	1.73	0.50–6.19
Male	10	10			
Female	11	19			
Age group (years)			0.499[b]	0.69	0.12–3.85
< 50	3	3			
≥ 50	18	26			
Duration of DM (years)			0.002[a]*	0.14	0.03–0.49
< 5	17	11			
≥ 5	4	18			
Smoking status			0.056[b]	1.88	1.47–2.61
No	21	24			
Yes	0	5			
Number of anti-diabetics			0.413[a]	1.63	0.55–6.22
1	14	16			
> 1	7	13			
Type of anti-diabetic					
Insulin	11	14			
Oral	9	12	0.483[a]	2.36	0.21–5.91
Combination	1	3	0.938[b]	1.05	0.33–3.38
Metabolic syndrome			0.432[a]	0.62	0.17–2.19
No	8	8			
Yes	13	21			
HbA1c (%)			0.621[b]	1.48	0.19–4.18
< 6,5	1	2			
≥ 6,5	20	27			
25 (OH) D (ng/ml)			0.661[a]	0.78	0.23–2.59
< 20	11	17			
≥ 20	10	12			

[a]Chi-Square Test; [b]Fisher's Test; *p < 0.05; RR = a / (a + b): c / (c + d).

Our study found that it was a significant association between duration of DM and DPN severity. Most of the subjects with a duration of DM < 5 years had mild DPN (17 subjects, 60.7%), but most of them with a duration of DM ≥ 5 years had severe DPN (18 subjects, 62.1%).

Table 3: Proportion Vitamin 25 (OH) D Level

Vitamin 25(OH)D Level (ng/ml)	Frequency	Percentage
<10 (severe deficient)	2	4
10–19.9 (deficient)	26	52
20–29.9 (insufficient)	21	42
≥30 (adequate)	1	2

In Table 3, almost all of the subjects had vitamin D deficiency (49 subjects, 98%). Most of them (26 subjects, 52%) had vitamin 25 (OH) D level 10 – 19.9 ng/ml (deficient).

In 3rd month, approximately 29 subjects (58%) had severe DPN, which 14 subjects (28%) had BDC 2. The proportion of DPN severity is shown in Table 4.

Table 4: Proportion of DPN Severity

DPN Severity	Frequency	Percentage
Mild		
BDC 1	21	42
Severe		
BDC 2	14	28
BDC 3	9	18
BDC 4	6	12

The predictive model analysed by logistic regression and cutoff point on the ROC curve was 4 (Figure 1). After 3 months, 24 subjects (75%) with predictive score > 4 had severe DPN and 13 subjects (72%) with predictive score ≤ 4 had mild DPN. The combination of predictive factors had strongly basic to estimate DPN severity after 3 months. The predictive model was more accurate than a predictive variable alone.

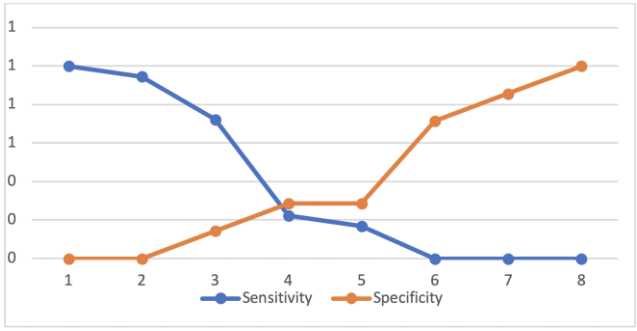

Figure 1: ROC Curve for Predictive Model

In Table 5, the predictive model had a sensitivity of 82.8% and specificity of 61.9%. Positive predictive value of 75%. Negative predictive value of 72.2%. Subjects with a score > 4 on this predictive model of DPN severity had relative risk (RR) of 2.70, that showed 2.7 times higher risk of severe DPN after 3 months.

Table 5: Comparison between Predictive Score and DPN Severity

		DPN Severity		Total	p	RR	95% CI
		Severe	Mild				
Predictive Score	≥ 4	24	8	32	0.001*	2.70	0.171–0.801
	≤ 4	5	13	18			
Total		29	21	50			

Chi-Square Test; *p < 0.05; RR = a / (a + b): c / (c + d).

Discussion

In this study, most of the subjects were female (60%) and belonged to ≥ 50 years old age-group (88%), with DM duration < 5 years (56%), had metabolic syndrome (68%) and had HbA1c level ≥ 6.5% (94%). Willer et al. 's study (2016) found risk factor of type 2 DM and its complications which is obesity and psychosocial stress appears to have a greater impact on women rather than on men [20]. The DN is commonest after 5th decade. Middle age / elderly diabetic was generally more affected [21]. Neuropathic symptoms increase with duration of DM [16], [21]. Some studies found a lower prevalence of DPN in those with duration < 5 years and the highest in those with duration > 15 years [7], [22]. Accumulating evidence suggests that the prevalence of DPN markedly elevated at the time of diabetes diagnosis [15]. Hyperglycemia, dyslipidemia, and metabolic syndrome have all been shown to initiate neuropathy through a common mechanism oxidative stress [15]. HbA1c as an indicator of glycemic control [22]. Poor glycemic control is regarded as the most important contributor to the mechanism of DN [11].

We found most of the subjects had vitamin 25 (OH) D level < 20 ng/ml (56%). Vitamin 25 (OH) D might play a functional role in glucose homeostasis. Vitamin D has a potential impact on insulin secretion, insulin sensitivity, and subsequently on the incidence of DM [11]. Patients with vitamin D deficiency (25 (OH) D < 20 ng/ml) had higher odds of having symptomatic DN than individuals with 25 (OH) D of 30 – 40 ng/ml [11], [12]. Vitamin D might be implicated in DPN's pathophysiology via its potential influence on nerve function [12].

In this study, most of the predictive factors were not significant association with DPN severity. But the combination of that variable in the predictive model was a significant association with DPN severity.

On this predictive model of DPN severity, subjects with a score of higher than 4 had RR of 2.70, showed that had 2.7 times higher risk of severe DPN than a score of lower as 4 after 3 months.

The predictive model had a sensitivity of 82.8% and specificity of 61.9%. The sensitivity of 82.8% was probability subjects had severe DPN with predictive score > 4 as 82.8%. The specificity of 61.9% was probability subjects had mild DPN with predictive score ≤ 4 as 61.9%. Positive predictive

value of 75%, was probability subjects with predictive score > 4 had severe DPN as 75%. Negative predictive value of 72.2%, was probability subjects with predictive score ≤ 4 had mild DPN as 72.2%.

In conclusion, a score of higher than 4 on this predictive model showed 2.7 times higher risk of severe DPN. A predictive model with using a scoring system in predicting DPN severity based on vitamin D level had high sensitivity and specificity.

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