Fibrinogen Function Indexs, Potential Biomarkers, are Closely Connected to Diabetic Peripheral Neuropathy

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Research Article

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Abstract

Background and Objectives: Research suggested that diabetic peripheral neuropathy (DPN) was related to plasma fibrinogen (Fib) concentration, while there was no research on the correlation with fibrinogen function. In this study, two indexes reflecting the function of plasma fibrinogen, k value and angle α, were used to analyze its correlation with DPN, and to explore the possibility of using them as biological indicators for diagnosing DPN.

Subjects and methods: This study is a prospective observational clinical study. About 561 T2DM patients were enrolled and divided into the diabetes with symptomatic neuropathy group (161 cases), the diabetes with asymptomatic neuropathy group (132 cases) and the diabetes with no neuropathy group (268 cases). Meanwhile, 160 healthy unrelated subjects were recruited as control group. The levels of k value and angle α were detected.

Results: The Fib levels increased slightly in diabetic subjects with neuropathy compared with those without. The angle α levels increased slightly in diabetic with asymptomatic neuropathy subjects compared with diabetes with no neuropathy subjects, and the levels increased greatly in diabetic subjects with symptomatic neuropathy compared with those without. The k value levels declined slightly in diabetic with asymptomatic neuropathy subjects compared with diabetes with no neuropathy subjects, and the levels declined greatly in diabetic subjects with symptomatic neuropathy compared with those without. The association of k value and angle α with diabetic neuropathy was independent of the hyperglycemic state (HbA1c, duration) and other potential confounders affecting k value and angle α levels (e.g., age, Fib, vitamin B12 and renal status) (odds ratio 0.080 [0.051–0.124], P= 0.001; odds ratio 1.131 [1.063–1.204], P= 0.001). In addition, k value and angle α levels were closely correlated to the stages of neuropathy (r= -0.686, P = 0.000; r= 0.314, P = 0.000). Meanwhile, the optimal cutoff point for k value levels to distinguish patients with diabetic neuropathy from those without was 1.8min, with a sensitivity of 73.7% and a specificity of 83.2% (AUC= 0.873). The optimal cutoff point for angle α levels was 60deg, with a sensitivity of 41.0% and a specificity of 95.6% (AUC= 0.669).

Conclusions: The levels of k value and angle α are closely associated with peripheral neuropathy in patients with diabetes. The levels of k value and angle α may be helpful for early diagnosis of diabetic peripheral neuropathy.

Background

Diabetic Mellitus (DM) has become the world's leading chronic non-communicable epidemic disease, with an average global prevalence rate of 8.6%. According to the World Health Organization, there are an estimated 451 million people with diabetes worldwide in 2017. It is estimated that the population of diabetes will reach 693 million by 2045 [1-3]. DM is the fifth leading cause of death in the world, while Diabetic peripheral neuropathy (DPN) is a common chronic complication of diabetes, with an incidence of 60% to 90%, and nearly 50.0% of patients have no symptoms [4], and there is a high rate of disability.

The currently accepted and reliable method for the diagnosis of DPN in the clinic are neuroelectrophysiological examination and small neurofibropathy examination [5, 6]. But the examination is relatively time consuming, laborious, and costly, and it requires a professional doctor and a physician who can issue a report. Therefore, it is less popular in the clinic. Some scholars tried to find serological markers for the diagnosis of DPN, such as NSE, Cys, TNF/TLR4 and TGF [7-9]. They have certain diagnostic value, but none of them have become recognized diagnostic indicators.

At present, DPN is associated with oxidative stress, metabolic abnormalities, immune and inflammatory responses [10]. At the same time, studies have also confirmed that neurological microcirculatory disorders are an important pathogenesis of it [11]. In recent years, studies have found that hemodynamic disorders are involved in the pathogenesis of DPN [12]. and plasma fibrinogen (Fib) is closely related to DPN [13-15]. In this regard, k value and angle α as the function of Fib may act as an ewemerging biomarker of peripheral neuropathy in diabetes. However, so far there is no report on the relationship between fib function and DPN. In addition, little data is available for the Chinese who are plagued by an increasing incidence of diabetes [16]. That is why we evaluated the relationship between k value, angle α and diabetic neuropathy.

1. Research Design And Method

1.1 General Information

561 subjects which all in line with the 1999 World Health Organization (WHO) type 2 diabetes diagnostic criteria registered consecutively as outpatients or inpatients with our hospital and 160 healthy control subjects registered with our hospital physical examination center between August 2018 and March 2021 were randomly enrolled into the study. All volunteers signed informed consent. The study was approved by the hospital and university scientific and ethic committees. Patients with age< 20 years or> 75 years, severe liver and kidney damage, trauma, surgery, pregnancy or lactation, diabetic ketosis, blood disease, long-term alcohol abuse, other non-diabetic causes (such as cerebral infarction, neck Lumbar disease, severe infection, poisoning, malnutrition, etc.) cause neurological damage, other diseases may be confused with clinical symptoms of DPN, such as vitamin deficiency, osteoarthritis, peripheral vascular disease, trauma surgery were excluded. The inclusion criteria of healthy control subjects include no history of diabetes, fasting blood glucose< 5.6mml/L, glycated hemoglobin< 5.6%.

1.2 Method

1.2.1 Neurological symptoms and physical examination

Testing was performed on each participant by the same experienced physician according to standard procedures. All tests were conducted in a quiet laboratory. At first, all patients had a complete history of neurological symptoms taken and were given a physical examination.

For somatic and cardioautonomic neuropathy, symptoms were documented, including numbness, asleep feeling, burning, deep aching, unsteadiness in walking, unexplained resting tachycardia and postural fainting [17].

Assessed by a professional medical staff (Toronto clinical score): 10g nylon wire (pressure sense), tuning fork (vibration sense), temperature sense, acupuncture pain, tendon reflex; 2 of the 5 tests have abnormal signs of the nervous system [18, 19].

1.2.2 Nerve conduction velocity tests and clinical feature measurement

All patients were examined using the EMG instrument (Keypoint 9033A07, Denmark). At the time of testing, the subjects were all in a quiet environment. The distal latency (DML), motor conduction velocity (MCV) and motor nerve conduction amplitude (CMAP) of the bilateral median nerve, ulnar nerve, tibial nerve and common personal nerves were detected respectively. The sensory conduction velocity (SCV) and sensory nerve action potential amplitude (SNAP) of bilateral median nerve, ulnar nerve, superficial peroneal nerve and sural nerve were detected respectively. At the same time, the bilateral tibial nerve H reflex and the ulnar nerve F wave latency were detected.

Body weight and upright height were measured on the same scales and wall-mounted stadiometer in light clothing and no shoes before breakfast. Individual BMI was then calculated as weight (kg)/height $(m)^2$. The right-arm blood pressure of each seated subject was obtained after 10 min of rest using a mercury sphygmomanometer. Retinal conditions were evaluated by ophthalmologists using a combination of clinical examination, stereoscopic retinal photographs, optical coherence tomography and fluorescein angiography.

All subjects stopped anticoagulant and antiplatelet drugs 2 weeks ago, and venous blood was collected in the morning through the elbow vein after fasting for 10 to 12 hours. K value and angle α were determined by thromboelastography analyzer (CFMS LBPU-8800; Lepu, Beijing). Fib was measured using blood coagulation meter (FAC21A-UW; Ltd, Taiwan). The fasting plasma glucose, serum creatinine, blood lipids, liver and kidney function were measured by an automatic biochemical analyzer (cobas 8000; Roche, Germany). HbA1c was measured using high-performance liquid chromatography (D10; Bio-Rad, Berkeley, CA). Serum vitamin B12 was measured using automated test assays (Maglumi 4000; China). Urinary albumin concentration was determined using immunonephelometry (DCA2000; Bayer, Leverkusen, North Rhine-Westphalia, Germany). Urinary creatinine concentrations were determined using the alkaline picrate method. The individual urinary albuminto-creatinine ratio (UACR) was then calculated as albumin (mg)/creatinine (g). The endogenous Ccr was calculated to estimate the glomerular filtration rate according to the Cockcroft equation: Ccr = {[140– age (years)× body weight (kg)]/[0.818× serum creatinine (Scr, umol/L)]} for male and the result× 0.85 for female.

1.2.2 Diagnosis and stages of polyneuropathy

Diabetic neuropathy was classified according to the American Diabetes Association recommendation [20]. Polyneuropathy was further staged into three groups. Group A (symptomatic neuropathy) was defined as the diabetes with symptomatic neuropathy group. Group B (asymptomatic neuropathy) was defined as the diabetes with asymptomatic neuropathy group. Group C (no neuropathy) was defined as the diabetes without neuropathy group. Group D (no neuropathy) was a healthy control group.

1.3 Statistical analysis

We used SPSS version 19 for software for statistical analysis. The data was expressed as the mean (SD) for normally distributed data. The chi-square test was used to compare the count data. The multiple comparisons among groups were assessed using one-way analysis and comparison between two groups (LSD method) for variables. The t test was used for comparison between the two groups. K value and angle α were later added to a logistic regression model, controlling for possible confounders for them. The relation of the k value and angle α levels to the stages of neuropathy was performed using spearman correlation analysis. Receiver operating characteristic (ROC) analysis was conducted with MedCalc Software version 15.2 to assess the accuracy of serum k value and angle α levels in distinguishing between patients with diabetic neuropathy and without. The optimal cutoff point was identified by calculating the area under the curve (AUC). $P< 0.05$ was considered statistically significant.

2. Results

The study was completed by 561 subjects, including 160 healthy control subjects, 293 diabetic subjects with neuropathy and 268 diabetic subjects without neuropathy (Table 1). Among the four groups of subjects, there were no differences between any given two groups in the following variables: sexratio, age, blood pressure, BMI, blood lipids (total cholesterol, LDL cholesterol, HDL cholesterol), liver and kidney function (ALT, AST, urinary ACR and Ccr), vitamin B12 and PLT. The incidence of diabetic retinopathy in patients with diabetic neuropathy was higher than in other groups. Comparison of different groups of diabetes, diabetes neuropathy group (group A) with the longest course in each group (Table 1). Symptomatic neuropathy was identified in diabetic subjects with increased levels of Fib compared with the patients without neuropathy and asymptomatic neuropathy. There was no significant decrease in the k value relative to the normal control group (group D) in the diabetic group without peripheral neuropathy (group C) ($P= 0.191$). K value was slightly reduced in the subclinical DPN group (group B) ($P= 0.001$), and further decreased in the confirmed DPN group (group A) ($P= 0.000$). Compared with the normal control group (group D), the angle α levels were not significantly increased in the diabetic non-peripheral neuropathy group (group C) ($P= 0.404$), but in the subclinical group (group B) and the confirmed DPN group (group A) there was a significant increase ($P= 0.000$), moreover the confirmed DPN group (group A) was significantly higher than the subclinical DPN group (group B) ($P= 0.002$)Table 2. The k value and angle α levels in relation to neuropathy were further assessed in a multivariate model (Table 3),

controlling for retinopathy and other covariables that may potentially influence the k value and angle α levels or neuropathy, which included disease course, age, HbA1c, eGFR, UACR, vitaminB12 and Fib. After adjustment, the k value and angle α were still independently associated with diabetic neuropathy respectively (odds ratio 0.080 [0.051–0.124], P = 0.000; odds ratio 1.131 [1.063–1.204], P = 0.000; respectively). Correspondingly, k value levels were negatively correlated with diabetic peripheral neuropathy (r= -0.656, P= 0.000). Angle α levels were positively correlated with diabetic peripheral neuropathy (r= 0.314, P= 0.000). Fib levels correlated with diabetic peripheral neuropathy (r = 0.252, P =0.000) (Table 3). K value and angle α levels were shown in distinguishing between patients with and without diabetic neuropathy. The optimal cutoff point of the k value and angle α levels respectively were 1.8 min and 58.4 deg, with a sensitivity of 73.7%, a specificity of 83.2%, the highest AUC equal to 0.873 (P= 0.001) and a sensitivity of 95.6%, a specificity of 41.0%, the highest AUC equal to 0.669 (P= 0.001) (Figure 1, Figure 2).

Table 1 Comparison of clinical features between different groups

Group	Case (male/female)	Age (years)	Disease course（years）
A	82/79	50.7±7.6	8.5±3.6
B	70/62	51.3±8.0	7.8±2.9
C	140/128	51.2±8.5	6.6±3.4
D	84/76	51.05±7.0	—
P value	0.145	0.839	0.000
Group	SBP (mmHg)	DBP (mmHg）	BMI (kg/m ^{2})
A	122±9	70±7	23.9±1.7
B	122±9	70±6	24.0±1.7
C	123±9	69±7	23.9±1.7
D	121±10	68±6	23.9±1.9
P value	0.476	0.206	0.928
Group	FPG (mmol/L)	HbA1c (%)	Total cholesterol（mmol/L）
A	8.3±1.7	8.2±1.3	4.9±0.8
B	8.2±1.7	8.2±1.4	4.9±0.6
C	8.4±1.4	8.0±1.5	4.8±0.7
D	4.8±0.5	4.8±0.5	4.8±0.9
P value	0.000	0.000	0.967
Group	LDL-C (mmol/L)	HDL-C (mmol/L)	ALT （IU/L）
A	2.7±0.9	1.4±0.4	23±3
B	2.7±0.9	1.3±0.4	24±2
C	2.8±0.7	1.4±0.4	24±3
D	2.6±0.7	1.4±0.4	23±4
P value	0.391	0.397	0.233
Group	AST （IU/L）	Vit B12 (pmol/L)	PLT (×10^9/L)

A	22±4	522±185	233±70
B	22±3	521±201	237±66
C	22±3	542±204	238±62
D	22±3	525±187	246±66
P value	0.411	0.607	0.329
Group	DR (%)	UACR (mg/g)	eGFR [ml/(min·1.73m^2)]
A	23.6	21.3±3.5	98.7±26.7
B	21.2	22.0±2.9	104.3±29.0
C	11.2	21.4±3.2	103.1±26.7
D	—	—	100.4±33.6
P value	0.002	0.101	0.291

Table 2 Comparison of k value, angle α and Fib between groups

Group	Fib（g/L）	K value (min)	Angle α (deg)
A	3.54±0.45	1.6±0.2	61.9±1.5
B	3.07±0.56	1.8±0.1	60.7±1.7
C	3.11±0.60	2.1±0.3	59.3±4.5
D	3.05±0.60	2.1±0.3	59.6±3.4
P value[1]	0.000	0.000	0.002
P value[2]	0.000	0.000	0.000
P value[3]	0.000	0.000	0.000
P value[4]	0.482	0.000	0.000
P value[5]	0.838	0.000	0.005
P value[6]	0.322	0.191	0.404

([1]*P*, diabetes with symptomatic neuropathy vs. diabetes with asymptomatic neuropathy. [2]*P*, diabetes with symptomatic neuropathy vs. diabetes without neuropathy. [3]*P*, diabetes with ymptomatic neuropathy vs.

healthy control. [4]*P*, diabetes with asymptomatic neuropathy vs. diabetes without neuropathy. [5]*P*, diabetes with asymptomatic neuropathy vs. healthy control. [6]*P*, diabetes without neuropathy vs. healthy control.)

Table 3 Multiple regression analysis of the relation of K value and angle α to neuropathy

Covariables	OR	95% CI	*P* value
Disease course	1.106	1.025–1.194	0.010
Age	0.985	0.959–1.011	0.254
HbA1c	1.100	0.944–1.282	0.220
DR (%)	1.219	0.617–2.409	0.569
eGFR	0.999	0.991–1.007	0.754
UACR	1.055	0.987–1.128	0.116
Vit B12	0.999	09984–1.001	0.319
Fib	1.543	1.069–2.227	0.021
Angle α	1.131	1.063–1.204	0.000
K value	0.080	0.051–0.124	0.000

Table 4 Correlation analysis between diabetic peripheral neuropathy and plasma k value and angle α (spearman correlation analysis)

Item	Angle α	K value	Fib
DPN			
r	0.314	-0.656	0.252
P value	0.000	0.000	0.000

3. Conclusions

The results of this study demonstrated that k value and angle α are potential biomarkers of DPN. In this study, patients with diabetic peripheral neuropathy have lower k value than diabetic patients without peripheral neuropathy and the levels of angle α in diabetic peripheral neuropathy are significantly higher than that in diabetic patients without peripheral neuropathy. More importantly, the k value and the angle α were changed in the early stage of diabetic peripheral neuropathy (subclinical diabetic peripheral neuropathy).

DPN refers to clinical and/or electrophysiological evidence of peripheral neuropathy, which must be clear of diabetes and exclude other diseases. The incidence of DPN can be as high as 60% to 90%, and the incidence rate reported in China is as high as 85%. At present, the pathogenesis of DPN is still not clear. Many studies suggest that DPN is associated with abnormal metabolic pathways, microvascular disease, nerve growth factor, autoimmunity, inflammation and oxidative stress. Among them, metabolic pathway abnormalities and microvascular changes are considered in DPN to play an important role in the occurrence and development [21, 22]. A large number of studies have shown that there are abnormalities in blood coagulation and fibrinolysis in diabetic patients, and a hypercoagulable state is present [23, 24]. In patients with diabetes, insulin resistance is present. When blood glucose control is poor, high insulin and high blood sugar levels increase the level of plasminogen activator inhibitors, and at the same time, the secretion of plasminogen activator inhibitors from vascular endothelial cells increases hypercoagulable state, which leads to the occurrence and development of diabetic peripheral neuropathy [25]. Fibrinogen is enhanced when there is hypercoagulability and hyperfibrinolysis in the blood. Erem C [26] found that patients with type 2 diabetes were hypercoagulable, and fibrinogen was significantly higher in patients with type 2 diabetes mellitus with peripheral neuropathy than in patients without neuropathy, which is consistent with the results of this study. However, the traditional fibrinogen assay can only detect the amount of fibrinogen after blood in vitro, but does not measure its function. The k value and angle α mainly reflect the fibrinogen function, and the high fibrinogen functional state is characterized by a shortened k value and an increased angle α. This study found that k value was lower in diabetic patients with peripheral neuropathy than in normal subjects and those without peripheral neurological complications. It suggests that the formation of fibrinogen is short and the speed is increased when diabetic peripheral neuropathy occurs. And angle α in diabetic patients with peripheral neuropathy is higher than that in normal people and those with simple diabetes, suggesting that fibrinogen function is enhanced when there are complications of peripheral neuropathy. Moreover, in this study, the k value and the angle α levels are closely related to the degree of diabetic neuropathy, and the k value levels are reduced in the subclinical diabetic peripheral neuropathy, and further decrease as the degree of diabetic peripheral neuropathy increases. The angle α levels increase as the degree of neuropathy increases. This relationship was independent of covariables.

Diabetic peripheral neuropathy has a high incidence, and its clinical symptoms are also diverse. Due to the low degree of early neurological damage in DPN, typical symptoms and signs are not significant, even without any symptoms. This is easily overlooked, and once the disease progresses, there may be adverse outcomes such as diabetic foot [27]. Therefore, the diagnosis of diabetic peripheral neuropathy, especially early diagnosis, is crucial.

At present, the methods for diagnosis of DPN commonly used in neuromuscular electromyography (neural conduction measurement), nerve biopsy, Toronto clinical score and Michigan neuropathy screening table have their limitations and low clinical promotion. According to different screening methods, the prevalence of DPN was 2.4-74.8% [28]. In contrast, serological diagnostic markers are more time-saving, labor-saving, low-cost, high clinical promotion, and do not require professional physicians to operate, but currently there are few studies on serological markers for early diagnosis of DPN (such as

cystatin C, NSE et al [6, 7]), and so far have not become the globally recognized indicators of DPN diagnosis [29]. In this study, we further confirmed that Fib was elevated in diabetic peripheral neuropathy. In addition, we found that k value and angle α were closely related to DPN, and there was a significant change in subclinical DPN. The results suggested that the sub-clinical DPN had a smaller k value and an increased angle α, which can provide a basis for the diagnosis of DPN earlier. At the same time, this study concluded that the optimal cutoff points for k value and angle α levels to distinguish patients with diabetic neuropathy from those without respectively were 1.8 min (≤ 1.8 min) and 58.4 deg (> 58.4 deg),. Neither of these two intercept points exceeds the reference range of k value and angle α (k: 1-3 min; angle α: 53-72 deg), which indicates that compared with patients with diabetic peripheral neuropathy, if the lower limit of the reference value range of k value is used as the reference boundary value to distinguish the presence or absence of diabetic peripheral neuropathy, it will be too low; if the upper limit of the reference range of the angle α is taken as the boundary value, it will be too high. This is not conducive to the early diagnosis of diabetic peripheral neuropathy.

In conclusion, this study further confirmed that abnormal blood coagulation may lead to the occurrence and development of diabetic peripheral neuropathy. The k value and the angle α serve as an indicator of coagulation function may provide a potential blood biomarker for the diagnosis and treatment of diabetic peripheral neuropathy. However, there are still some limitations to this study. The sample size of this study is not large, which may have an impact on the research. Further comprehensive research on large samples is needed.

Declarations

The study was approved by the hospital and university scientific and ethic committees. All volunteers agreed and signed informed consent.

All authors agree to publish it.

The datasets used or analysed during the current study are available from the corresponding author on reasonable request.

No potential conflicts of interest relevant to this article were reported.

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Xiahong Lin designed the study and contributed to discussion. Yong Zhuang wrote, reviewed, edited the manuscript and is the guarantor of this work and, such as, had full access to all the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis. Xiaoyu Chen and Xiaohong Wu collected and researched data. Jinying Zhang reviewed the manuscript.

References

1. Xu Y, Wang L, He J, et al. Prevalence and Control of Diabetes in Chinese Adults [J]. Jama, 2013, 310 (9): 948-959. DOI: 10.1001/jama.2013.168118.
2. Yang W, Lu J, Weng J, et a1. Prevalence of diabetes among men and women in China [J]. N Engl J Med, 2010, 362 (12): 1090-1101. DOI: 10.1056/NEJMoa0908292.
3. Cho NH, Shaw JE, Karuranga S, et al. IDF Diabetes Atlas: Global estimates of diabetes prevalence for 2017 and projections for 2045 [J]. Diabetes Res Clin Pract. 2018 Apr; 138:271-281. DOI: 10.1016/j.diabres.2018.02.023.
4. Boulton AJM, Armstrong DG, Kirsner RS, et al. Diagnosis and Management of Diabetic Foot Complications [M]. Arlington (VA): American Diabetes Association; 2018 Oct. DOI: 10.2337/db20182-1.
5. Thabit MN, Sedky A, Sayed MA et al. Double-Shock Stimulation of the Superficial Radial Nerve Compared With Standard Medial Plantar Nerve Conduction in the Early Detection of Asymptomatic Diabetic Neuropathy: A Pilot Study [J]. J Clin Neurophysiol. 2018 Nov; 35(6): 474-480. DOI: 10.1097/WNP.0000000000000522.
6. Selvarajah D, Kar D, Khunti K, et al. Diabetic peripheral neuropathy: advances in diagnosis and strategies for screening and early intervention [J]. Lancet Diabetes Endocrinol. 2019 Dec;7(12):938-948. DOI: 10.1016/S2213-8587(19)30081-6.
7. Li J, Zhang H, Xie M, et al. NSE, a potential biomarker, is closely connected to diabetic peripheral neuropathy [J]. Diabetes Care. 2013 Nov; 36(11): 3405-10. DOI: 10.2337/dc13-0590.
8. Hu Y, Liu F, Shen J, et al. Association between serum cystatin C and diabetic peripheral neuropathy: a cross-sectional study of a Chinese type 2 diabetic population [J]. Eur J Endocrinol. 2014 Nov; 171(5): 641-8. DOI: 10.1530/EJE-14-0381.
9. Zhu T, Meng Q, Ji J, et al. Toll-like receptor 4 and tumor necrosis factor-alpha as diagnostic biomarkers for diabetic peripheral neuropathy [J]. Neurosci Lett. 2015 Jan 12;585:28-32. DOI: 10.1016/j.neulet.2014.11.020. Epub 2014 Nov 17.
10. Hussain G, Rizvi SA, Singhal S, et al. Serum levels of TGF-β1 in patients of diabetic peripheral neuropathy and its correlation with nerve conduction velocity in type 2 diabetes mellitus [J]. Diabetes Metab Syndr. 2016 Jan-Mar; 10 (1 Suppl 1): S135-9. DOI: 10.1016/j.dsx.2015.10.011.
11. Hile C, Veves A. Diabetic neuropathy and microcirculation [J]. Curr Diab Rep. 2003 Dec;3(6):446-51. DOI: 10.1007/s11892-003-0006-0.
12. Gholami F, Nikookheslat S, Salekzamani Y et al. Effect of aerobic training on nerve conduction in men with type 2 diabetes and peripheral neuropathy: A randomized controlled trial [J]. Neurophysiol Clin. 2018 Sep; 48(4): 195-202. DOI: 10.1016/j.neucli.2018.03.001.
13. Carr ME. Diabetes mellitus: a hypercoagulable state [J]. J Diab Complic, 2001 Jan-Feb; 15(1): 44-54.
14. Coban E, Sari R, Ozdogan M, et al. Levels of plasma fibrinogen and d-dimer in patients with impaired fasting glucose [J]. Exp Clin Endocrinol Diabetes. 2005 Jan; 113(1): 35-7. DOI: 10.1055/s-2004-830524.

15. Sytze Van Dam P, Cotter MA, Bravenboer B, et al. Pathogenesis of diabetic neuropathy: focus on neurovascular mechanisms [J]. Eur J Pharmacol. 2013 Nov 5; 719(1-3): 180-6. DOI: 10.1016/j.ejphar.2013.07.017.
16. Yang W, Lu J, Weng J et al. Prevalence of diabetes among men and women in China [J]. N Engl J Med. 2010 Jun 24;362(25):2425-6;
17. Dyck PJ, Sherman WR, Hallcher LM, et al. Human diabetic endoneurial sorbitol, fructose, and myo-inositol related to sural nerve morphometry [J]. Ann Neurol. 1980 Dec;8(6):590-6. DOI: 10.1002/ana.410080608.
18. Zhao Z, Ji L, Zheng L, et al. Effectiveness of clinical alternatives to nerve conduction studies for screening for diabetic distal symmetrical polyneuropathy: A multi-center study [J]. Diabetes Res Clin Pract. 2016 May; 115:1 50-6. DOI: 10.1016/j.diabres.2016.01.002.
19. Yuan H, Zhang J, Tian R, et al. Evaluating the usefulness of the diabetic peripheral neuropathy screening process [J]. J Diabetes Metab, 2012, S5: 007. DOI:10.4172/2155□6156.S5□007.
20. Summary of revisions for the 2006 Clinical Practice Recommendations. Diabetes Care. 2006 Jan; 29 Suppl 1: S3.
21. Yang CP, Lin CC, Li CI, et al. Cardiovascular Risk Factors Increase the Risks of Diabetic Peripheral Neuropathy in Patients With Type 2 Diabetes Mellitus: The Taiwan Diabetes Study [J]. Medicine (Baltimore), 2015 Oct; 94(42): e1783. DOI: 10.1097/MD.0000000000001783.
22. Kwai NC, Nigole W, Poynten AM, et al. The Relationship between Dyslipidemia and Acute Axonal Function in Type 2 Diabetes Mellitus In Vivo [J]. PLoS One□2016 Apr 14; 11(4): e0153389. DOI: 10.1371/journal.pone.0153389.
23. Coban E, Sari R, Ozdogan M, et al. Levels of plasma fibrinogen and d-dimer in patients with impaired fasting glucose [J]. Exp.Clin Endocrinol Diabetes. 2005 Jan; 113(1): 35-7. DOI: 10.1055/s-2004-830524.
24. Behl T, Velpandian T, Kotwani A. Role of altered coagulation-fibrinolytic system in the pathophysiology of diabetic retinopathy [J]. Vascul Pharmacol. 2017 May; 92:1-5. DOI: 10.1016/j.vph.2017.03.005.
25. [25 Carr ME Jr, Alving BM. Effect of fibrin structure on plasmin-mediated dissolution of plasma clots [J]. Blood Coagul Fibrinolysis. 1995 Sep; 6(6):567-73.
26. Erem C, Hacihasanoğlu A, Celik S, et al. Coagulation and fibrinolysis parameters in type 2 diabetic patients with and without diabetic vascular complications [J]. Med Princ Pract. 2005 Jan-Feb; 14(1): 22-30. DOI: 10.1159/000081919.
27. Boulton AJM, Armstrong DG, Kirsner RS, et al. Diagnosis and Management of Diabetic Foot Complications [M]. Arlington (VA): American Diabetes Association; 2018 Oct. DOI: 10.2337/db20182-1.
28. Iftikhar M, Hussain A, Rizvi A. Frequency of peripheral neuropathy in patients with diabetes mellitus [J]. J Ayub Med Coll Abbottabad. 2014 Oct-Dec; 26(4):584-6.

29. Kwok T, Ting PT, Wong EK, et al. Peripheral neuropathy for dermatologists: what if not diabetic neuropathy? [J] J Cutan Med Surg. 2013 Oct; 17 Suppl 1: S1-5. DOI: 10.2310/7750.2013.WOUND3.

Figures

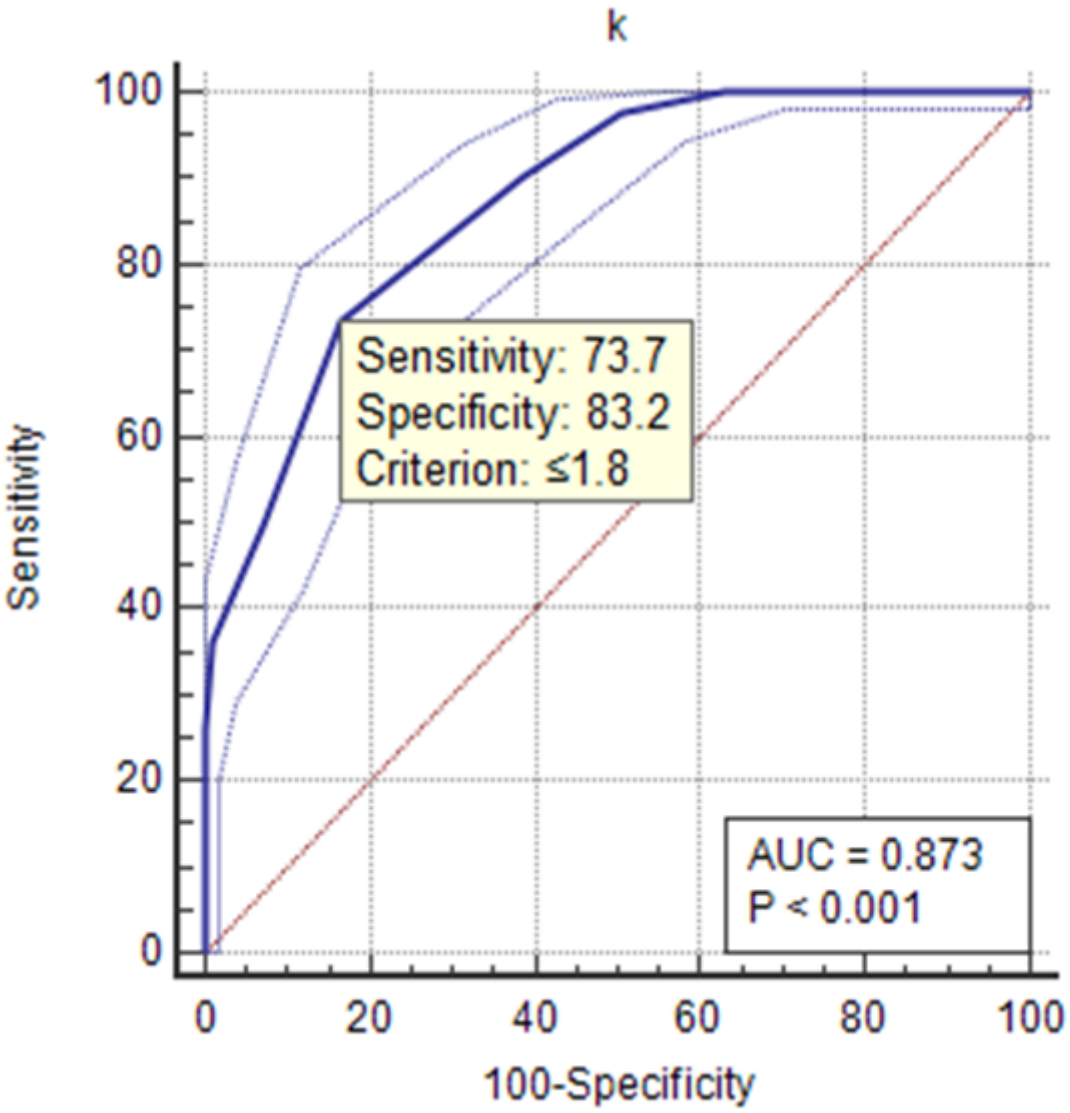

Figure 1

ROC plot (k value).

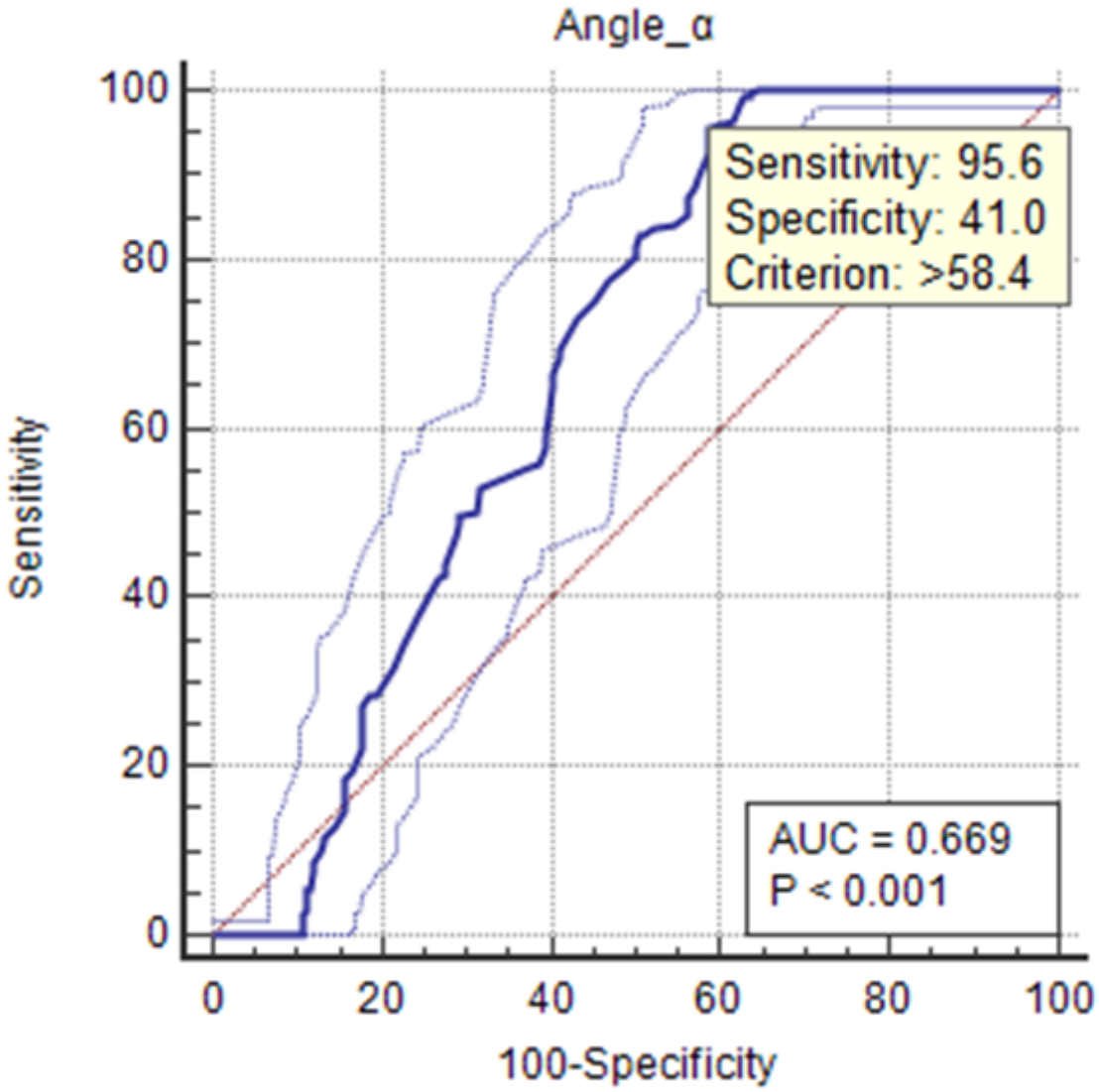

Figure 2

ROC plot (angle α).