Scientific Research Publishing

Yangtze Medicine, 2021, 5, 43-53
https://www.scirp.org/journal/ym
ISSN Online: 2475-7349
ISSN Print: 2475-7330

Influence of Metabolic Syndrome on Vibration Perception Threshold in First-Degree Relatives of Type 2 Diabetes Mellitus

Lili Yang[1*], Peng Yun[1*], Dan Liu[1], Zhen Zhang[1], Xuemei Yu[2], Fangping Li[1#]

[1]Department of Endocrinology, The Seventh Hospital Affiliated to Sun Yat-sen University, Shen zhen, China
[2]Department of Endocrinology, South Campus, Sixth People's Hospital, Shanghai Jiao tong University, Shanghai, China
Email: #lifangp01@163.com

How to cite this paper: Yang, L.L., Yun, P., Liu, D., Zhang, Z., Yu, X.M. and Li, F.P. (2021) Influence of Metabolic Syndrome on Vibration Perception Threshold in First-Degree Relatives of Type 2 Diabetes Mellitus. *Yangtze Medicine*, **5**, 43-53.
https://doi.org/10.4236/ym.2021.51005

Received: July 11, 2019
Accepted: January 10, 2021
Published: January 13, 2021

Abstract

Objectives: To investigate influence of metabolic syndrome on vibration perception threshold in first-degree relatives of type 2 diabetes who were not diagnosed with diabets before. **Material and Methods**: First-degree relatives of type 2 diabetes at the age of 40 - 60 s who had not been diagnosed with diabetes before were enrolled. Height, weight, waist circumference, hip circumference, blood pressure (systolic and diastolic blood pressure), body fat percentage, fasting plasma lipid, fasting plasma glucose, 2-hour blood glucose after 75 g oral glucose and vibration perception threshold were measured. **Results:** 58 subjects were diagnosed with the level of vibration perception threshold ≥ 16 V. Vibration perception threshold in the metabolic syndrome group was significantly higher than that in the non-metabolic syndrome group ($P < 0.05$). Vibration perception threshold increased with the increase of metabolic syndrome component. The group with ≥3 components of metabolic syndrome had a significantly higher level of vibration perception, as compared with that of group with 0 component, group with 1 component of metabolic syndrome ($p < 0.01$). Group with 2 components of metabolic syndrome had a significantly higher level of vibration perception threshold when comparing with group with 0 component ($P < 0.05$). Vibration perception threshold was positively correlated with weight, body mass index, waist circumference, systolic blood pressure, diastolic blood pressure, fasting plasma glucose and 2-hour blood glucose. Stepwise multiple regression analysis showed that there was a positive correlation between waist circumference, systolic blood pressure and vibration perception threshold. **Conclusion:** Some first-degree relatives of type 2 diabetes who have not been diagnosed with diabetes have high risk of peripheral neuropathy, especially those with

*Lili Yang and Peng Yun are co-first author.

metabolic syndrome. Waist circumference and blood pressure are the main factors affecting Vibration perception threshold levels. Early detection of vibration perception threshold should be performed in first-degree relatives of type 2 diabetes with metabolic syndrome. Waist circumference and blood pressure may be important risk factors of peripheral neuropathy for them.

Keywords

Metabolic Syndrome, Vibration Perception Threshold, Diabetes Mellitus

1. Introduction

Peripheral neuropathy (PN) is a common complication of diabetes whose onset is always insidious. When clinical symptoms appear, peripheral nerves have undergone irreversible segmental demyelination and other pathological changes, such as foot ulcers, ulceration and necrosis necessitating limb amputations, which seriously affect the therapeutic effect and life quality. The vibration perception threshold (VPT) in lower extremity is a sensitive predictor of distal symmetric peripheral neuropathy, whose sensitivity and specificity are high, and its sensitivity increases with age [1]. It is suspected that blood glucose and blood lipids may be involved in the PN pathogenesis. Abnormal lipid metabolism is an independent risk factor and is closely related to oxidative stress, insulin resistance, and hyperuricemia [2]. First-degree relatives that are the parents, children, biological brothers or sisters of type 2 diabetes mellitus (FDRs) have same genetic background with patients with type 2 diabetes (T2DM). At present, the population of FDRs is larger, who are more prone to metabolic disorders, and always with dyslipidemia, hyperuricemia, insulin resistance, and blood glucose fluctuations although have not diagnosed with Diabetes. As far as we know, the occurrence of peripheral neuropathy is related to many factors. Then, whether there is VPT abnormality in FDR not diagnosed with diabetes before, and what may affect VPT, there are few studies in the past. This study is to investigate the VPT status and its influencing factors of FDR.

2. Materials and Methods

2.1. Patients and Samples

We performed an observational study in the first-degree relatives of T2DM treated in our department from September 2013 to September 2014, and 405 FDR at the age of 40 - 60 s who had not been diagnosed with diabetes before were enrolled. The exclusion criteria were: with peripheral neuropathy caused by genetics, drugs, surgery, trauma and other diseases, recent trauma, infection, surgery and other stress condition, accompanied by liver and kidney disease, with cancer.

2.2. Clinical and Biochemical Measurements

1) Questionnaires were used to collect all participants' age, medical history, and smoking and drinking habits. Physical examination included measurements of height, weight, waist circumference (WC), hip circumference (HC) and blood pressure. Height was measured after taking off the shoes. Weight was measured after taking off the coat, shoes and taking out the weight in the pocket. A single examiner used a standard measuring tape to measure WC twice at 1.0 cm horizontally above the navel of the participant who was standing and wearing light-weight clothing and after inhalation and exhalation. HC was horizontally measured in the maximum hip circumference. Blood pressure (systolic pressure (SBP), diastolic pressure (diastolic pressure (DBP)) was measured three times for all participants who were seated, after a 5-min rest, by use of an electronic sphygmomanometer (Omron, HEM-770AFuzzy, Kyoto, Japan). The percentage of body fat (Fat %) was measured by bioelectrical impedance method.

2) Overnight fasting blood samples were collected and stored at −20˚C for measuring fasting glucose (FPG), triglycerides (TG), serum total cholesterol (TC), low-density lipoprotein cholesterol (LDL-C), high-density lipoprotein cholesterol (HDL-C), alanine aminotransferase (ALT), aspartate aminotransferase (AST), blood uric acid (UA), creatinine (Cr), urea nitrogen (BUN)) by use of an automatic biochemical analyzer (Beckmann DXC800, USA), HbA1c (high pressure liquid phase method) and 2 hours after oral administration of 75 g of glucose were also measured.

3) Vibration perception thresholds were measured at multiple frequencies using a Digital Vibration Sensing Threshold Checker (Sensiometer A, China) in accordance with previously described technique [3]. Subjects were trained by the examiner to experience a vibration first: firstly adjusted the vibration head of the handle to a state of obvious vibration, and then tested in the osseous part of the upper limb of the subject, so that the subject could tell the correct vibration feeling. Then, the vibration head was adjusted to a non-vibrating state test to confirm that the subject could correctly distinguish the difference between the vibration sensation and the normal pressure sensation. Subjects were allowed to relax and lie flat on the test, and then were instructed to inform the examiner immediately when they first felt a shock. The examiner touched the probe perpendicularly to the back of the big toe of the subject and rotated the control button. The amplitude of the vibration gradually increased from "0", letting the patient concentrate on the measurement point until the fixed point where the vibration just felt is Sensitive threshold. Detected twice in succession and averaged as the final test result.

Modified criteria of the "International Diabetes Federation (IDF) to diagnose MetS in adults" [4]: central obesity (waist circumference ≥ 90 centimeter in men and ≥85 centimeter in women) and any two of the following factors: raised triacylglycerol level ≥ 1.7 mmol/l, reduced HDL-cholesterol level ≤ 1.03 mmol/l, raised blood pressure (systolic ≥ 130 mmHg and/or diastolic ≥ 85 mmHg), and

raised fasting plasma glucose ≥ 5.6 mmol/l or diagnosed type 2 diabetes.

All subjects were equally divided into three groups by the vibrations thresholds [*i.e.* VPT6.05 V - 10.20 V (group 1), VPT 10.25 V - 12.45 V (group 2), VPT 12.50 V - 26.85 V (group 3)]. All subjects were also divided by metabolic syndrome components (*i.e.* MS group and non-MS group; group with 0 MS component, group with 1MS component, group with 2 MS components, group with ≥3 MS components).Results were presented as mean ± SD. Independent t-tests and x^2 were performed for comparisons of general characteristics of participants between the two groups. Multiple groups were compared using analysis of variance of completely random design data. Comparison between each group was performed using the least significant difference method (LSD). Pearson correlation analysis was performed for correlation analysis and multiple linear stepwise regression analysis were performed for multivariate analysis. Statistical significance was defined as P value < 0.05.

3. Results

3.1. General Characteristics of Subjects

Of all subjects, 186 (45.9%) with hypercholesterolemia, 118 (29.1%) with hypertriglyceridemia, 106 (26.2%) with high LDL-Cemia, and 54 with low HDL-Cemia (13.3%),118 with hypertension (29.1%), 58 with diabetes (14.3%), 48 with impaired fasting glucose (11.9%), 91 with impaired glucose tolerance (22.5%), 57 with VPT 16 - 25 V (14.07%),and 1with VPT > 25 V (0.25%).

The correlation between VPT on the left and right sides was good (r = 0.911, P < 0.05), so the average VPT on both sides was used for analysis. After being divided into three equal divisions according to VPT levels, the age, proportion of patients with dyslipidemia, proportion of patients with hypertension (respectively 23.7%, 28.2%, 30.4%), proportion of patients with diabetes (9.6%, 13.3%, 20.0%), proportion of smokers, proportion of drinking, BMI, Fat%, waist circumference, hip circumference, UA, Cr, CHO, LDL-C, FPG, 2h-PG, HbA1c, SBP, and DBP increased with the increase of VPT levels. There were significant differences in age, proportion of patients with hypertension, proportion of patients with diabetes, waist circumference, HbA1c, CHO, SBP and DBP (P < 0.05) (**Table 1**).

3.2. The Clinical Characteristics of MS and Non-MS Groups

Compared with non-MS group, the MS patients had significantly higher age and VPT (P < 0.05). There was a significant metabolic disturbance in the MS group (**Table 2**).

Comparison of VPT levels in patients with different metabolic components with the increase of metabolic components, VPT levels gradually increased, and there was a significant difference between MS0 group and MS1 group, as well as MS1 group and MS ≥ 3 group (P < 0.01). There was also significant difference between MS0 group and MS2 group (P < 0.05) (**Figure 1**).

Table 1. Relationship between VPT level and each indicator.

Group	I[a]	II[b]	III[c]	*F* or x^2	*P*-value
Cases (Male/Female)	135 (47/88)	135 (52/83)	135 (51/84)	0.444	>0.05
Age (years)	47.43 ± 5.82	49.12 ± 5.79	52.54 ± 5.64	9.56	<0.05
BMI (Kg/m^2)	24.3 ± 3.0	24.6 ± 2.6	24.9 ± 2.6	1.28	>0.05
WC (cm)	81.58 ± 9.23	83.19 ± 8.32	84.41 ± 8.98	3.388	<0.05
HC (cm)	91.30 ± 6.22	91.56 ± 5.77	92.63 ± 5.92	1.859	>0.05
Fat (%)	31.78 ± 6.77	32.00 ± 6.51	32.26 ± 6.62	0.489	>0.05
Smoking (Y/N)	22/113	30/105	36/99	4.287	>0.05
Drinking (Y/N)	23/112	19/116	22/113	0.481	>0.05
ALT (U/L)	27.99 ± 1.61	24.94 ± 1.56	25.38 ± 1.64	1.056	>0.05
AST (U/L)	23.99 ± 3.78	22.05 ± 3.71	23.58 ± 3.53	2.522	>0.05
UA (umol/l)	264.18 ± 42.13	272.27 ± 35.95	275.25 ± 41.29	0.347	>0.05
Cr (umol/l)	59.22 ± 12.58	60.01 ± 14.10	60.46 ± 12.90	0.688	>0.05
BUN (mmol/l)	4.58 ± 1.13	4.54 ± 1.26	4.77 ± 1.08	0.330	>0.05
SBP (mmHg)	122.39 ± 15.98	124.51 ± 18.28	128.15 ± 17.13	3.813	<0.05
DBP (mmHg)	79.50 ± 9.49	80.76 ± 11.63	82.17 ± 10.88	2.06	>0.05
CHO (mmol/l)	5.09 ± 1.06	5.15 ± 1.04	5.23 ± 1.02	9.56	<0.05
TG (mmol/l)	1.65 ± 0.14	1.55 ± 0.19	1.56 ± 0.18	1.453	>0.05
HDL (mmol/l)	1.28 ± 0.23	1.29 ± 0.24	1.28 ± 0.24	1.003	>0.05
LDL (mmol/l)	2.94 ± 0.72	2.95 ± 0.77	3.06 ± 0.71	1.114	>0.05
FPG (mmol/l)	5.53 ± 1.37	5.62 ± 1.29	5.88 ± 1.25	6.062	<0.05
2h-PG (mmol/l)	7.64 ± 1.66	7.65 ± 1.60	8.71 ± 2.18	3.399	<0.05
HbA1c (%)	5.60 ± 0.89	5.72 ± 0.96	5.88 ± 0.99	3.215	<0.05

a: Group I: VPT 6.05 V - 10.20 V; b: Group II: VPT 10.25 V - 12.45 V; c: Group III VPT 12.50 V - 26.85 V.

Table 2. Comparison between MS group and non-MS group.

Group	MS group	Non-MS group	x^2 or *t*	*P*-value
Cases (Male/Female)	120 (36/84)	285 (114/171)	3.205	>0.05
Age (years)	51.10 ± 5.27	49.13 ± 6.27	2.93	<0.01
Weight (Kg)	68.54 ± 10.98	61.70 ± 10.44	5.92	<0.01
BMI (Kg/m^2)	26.3 ± 3.0	23.9 ± 1.7	6.99	<0.01
wc (cm)	89.63 ± 7.30	80.23 ± 7.90	11.00	<0.01
hc (cm)	94.85 ± 6.59	90.53 ± 5.21	6.36	<0.01
HDL (mmol/l)	1.24 ± 0.26	1.30 ± 0.22	-2.17	<0.05
CHO (mmol/l)	5.24 ± 1.26	5.12 ± 0.94	0.90	>0.05
FPG (mmol/l)	5.94 ± 1.29	5.53 ± 1.36	3.40	<0.01
2h-PG (mmol/l)	9.24 ± 2.49	7.48 ± 1.75	3.83	<0.01
HbA1C (%)	5.95 ± 0.97	5.64 ± 0.94	3.042	<0.01
ALT (U/L)	27.94 ± 5.38	28.31 ± 4.32	0.154	>0.05
AST (U/L)	23.21 ± 5.21	22.91 ± 4.45	0.301	>0.05
Cr (umol/l)	57.61 ± 11.57	60.68 ± 14.03	1.568	>0.05
UA (umol/l)	287.82 ± 45.98	271.51 ± 41.89	1.803	>0.05
Fat (%)	35.49 ± 5.58	30.62 ± 6.50	6.614	<0.01
VPT (V)	12.19 ± 3.56	11.38 ± 2.93	2.416	<0.05

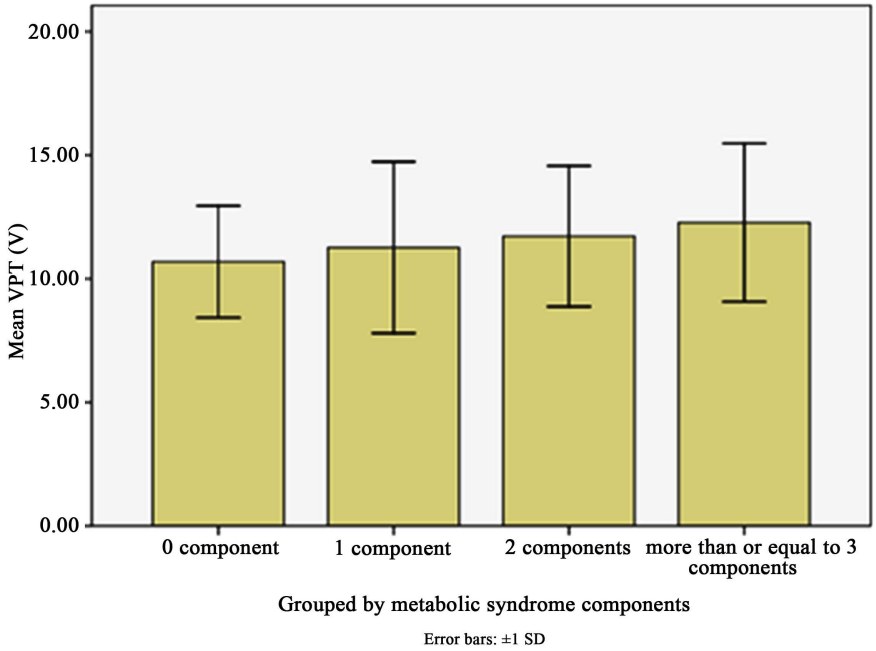

Figure 1. Vibrational sensory threshold changes with metabolic components. There was significant difference between MS0 group and MS1 group (P > 0.01); There was significant difference MS1 group and MS ≥ 3 group (P > 0.01); There was also significant difference between MS0 group and MS2 group (P < 0.05).

3.3. Analysis of Influencing Factors in VPT

Taking VPT as the dependent variable, BMI, waist circumference, hip circumference, SBP, DBP, TG, LDL, HDL, CHO, FPG, 2h-PG, HbA1c, and Fat% as independent variables, Pearson correlation analysis was performed. It was showed that there was a positive correlation between VPT and weight, BMI, waist circumference, SBP, DBP, FPG and 2h-PG. The difference was statistically significant (**Table 3**).

Multiple stepwise regression analysis showed that waist circumference and systolic pressure were positively correlated with VPT (r = 0.182, P < 0.01; r = 0.211, P < 0.01), and the regression equation was:

$$Y = 5.191 + 0.049X_1 + 0.019X_2$$

4. Discussion

Symptomatic pain and paresthesia are clinically present in PN, and approximately 50% of patients with PN are asymptomatic, wihch may leading to non-sensory damage to foot and is a major risk factor for foot ulceration, infections, and gangrene [5]. Nerve conduction velocity examination is currently the "gold standard" for diagnosis of PN, but it requires specialist's operation, which is time-consuming, labor-intensive, and costly, thus is difficult to applied extensively in large-scale screening and outpatient clinics [6]. Determination of VPT using a biothesiometer is a quick and easy way for detecting large-fiber dysfunction and identifing patients at risk of foot ulceration, lower-limb amputation. Its

Table 3. Pearson correlation analysis between VPT and each metabolic indicator.

	r	*P*-value
BMI	0.106	0.029
WC	0.131	0.010
HC	0.091	0.070
SBP	0.136	0.007
DBP	0.191	0.043
TG	0.043	0.370
LDL	0.090	0.062
HDL	0.022	0.644
CHO	0.075	0.120
FPG	0.206	0.000
2h-PG	0.117	0.018
HbA1c	0.132	0.008
Fat%	0.094	0.078

operation is simple, fast, painless, and well tolerated which is not affected by the temperature of the ankles and limbs. There is a standardized test algorithm, which is not only better than using a tuning fork. The sensory threshold of vibration is simple and accurate, and it can detect the trend of sensory changes in the nervous system. It is a popular method in PN assessment and research [7] [8] [9] [10]. Jia *et al.* [11] found that the consistency between VPT examination and nerve conduction velocity examination was good by evaluating the sensitivity, specificity, accuracy, and clinical applicability of the simple method for diagnosing PN. In a word, VPT examination can be used as a simple neuropathy method in outpatient and epidemiological investigations [6].

There have been many studies in the past to investigate the peripheral neuropathy in diabetic patients. However, studies have suggested that blood glucose control does not delay the development of PN in type 2 diabetic patients with peripheral neuropathy that has already occurred. [12] Impaired fasting glucose or impaired glucose tolerance may be associated with increased risk of peripheral neuropathy [13] [14]. At the same time, the American Diabetes Association recommends that early diet and exercise intervention in prediabetes patients may be the best way to prevent PN. Therefore, it is especially important to study VPT and its influencing factors in patients with high risk of hyperglycemia for early diagnosis and prevention of this disease.

Type 2 diabetes is a multifactorial disease associated with both genetic and environmental factors. FDR has a similar genetic background and similar living environment with patients with type 2 diabetes, thus the incidence of diabetes is significantly increased. Even without diabetes, FDR has significantly higher blood glucose and BMI than non-FDR [15]. At the same time, study found that

in individuals with a family history of young-onset, over 20% of siblings with an average age of 40 years had diabetes and 25% had prediabetes. After a decade, over one-fifth of those who were initially euglycaemic had developed Type 2 diabetes [16]. Previous studies have demonstrated that continuous glucose monitoring could identify the presence of significant dysglycaemia in FDR who were categorized as having normal glucose tolerance according to the OGTT [17]. Deepak Kumar Dash *et al.* found that subjects with DM history of family have increased BMI, worse Glycemic prfile, higher insulin resistance, increased SBP, higher adiposity indices and hsCRP. [18] So, how is the risk of PN in FDR those with high risk of diabetes? Previous studies mostly reflected the risk of PN in people with T2DM, and rarely studied PN in FDR not diagnosed with diabetes before. We conducted a VPT test on FDR and found that 14.32% of non-diabetic FDR had intermediate to high risk of PN. At the same time, our results suggest that the VPT of MS patients in FDR was significantly higher than that of non-MS subjects, and VPT was significantly increased with the increase of metabolic components. Weight, BMI, waist circumference, SBP, DBP, FPG, 2h-PG and other metabolic indicators all affect VPT. The effect of metabolic syndrome and its components on VPT is similar to that of previous studies. Callaghan BC [19] found in a cohort study of 2382 subjects that metabolic syndrome components were associated with PN independent with glycemic status. Similarly, Cortez M. [20] and his teamers believe that the baseline neuropathy is most strongly related to two or more components of the metabolic syndrome, not depending on blood glucose status. At the same time, Lee CC and his team [21] found in a 3-year follow-up study that the incidence of PN was highest in participants developed into type 2 diabetes 3 years later, followed by those who developed prediabetes and those with normal blood glucose had the lowest incidence. In addition, Shen Qin *et al.* [22] found that in the Shanghai community, there was a high prevalence of PN in pre-diabetes patients.

The exact mechanism of the relationship between various metabolic factors and PN is not yet clear. It may be related to the effects on blood vessels and nerves. Hypertension can cause hyaline degeneration of small arteries and necrosis of small blood vessels, accelerating the hardening of small arteries and damage of the vascular endothelium [23]. Metabolic syndrome is a common vascular risk factor and oxidative stress is greatly increased in patients with metabolic syndrome. El Boghdady NA [24] suggested that oxidative stress markers and vascular risk factors may be involved in the pathogenesis of peripheral neuropathy. Brownlee M. [25] *et al.* believe that excessive peroxide production is the key to induce various diabetic complications including PN. In addition, it may also be related to neurotrophic factors. Groover AL [26] found that after 2 weeks and 10 weeks of high-fat diet, although the mice have not yet reached diabetes, weight, blood glucose and insulin levels have increased sharply. The expression of neurotrophin protein in peripheral tissues and the composition of epidermal innervation have changed, which is closely related to the occurrence of peripheral neuropathy.

5. Conclusion

Our study shows that some of the FDRs that have not diagnosed with diabetes have a high risk of DN, especially in patients with MS. Waist circumference and blood pressure are main factors affecting VPT. It suggests that in FDR, MS patients are more likely to have peripheral neuropathy. Early detection of VPT should be performed in these people. Meanwhile, waist circumference and blood pressure may be important risk factors for peripheral neuropathy (PN) in FDRs.

Data Availability

The data used to support the findings of this study are available from the corresponding author upon request.

Approved

This study was approved and agreed by the Ethics Committee.

Conflicts of Interest

The authors declare that there is no conflict of interest regarding the publication of this paper.

References

[1] Martin, C.L., Waberski, B.H., Pop-Busui, R., Cleary, P.A., Catton, S., Albers, J.W., Feldman, E.L. and Herman, W.H. (2010) Vibration Perception Threshold as a Measure of Distal Symmetrical Peripheral Neuropathy in Type 1 Diabetes. *Diabetes Care*, **33**, 2635-2641. https://doi.org/10.2337/dc10-0616

[2] Yu, H. and Liu, J. (2011) Effect of Hyperuricemia on Peripheral Neuropathy in Patients with Type 2 Diabetes Mellitus and Its Relationship with Insulin Resistance. *Chinese Journal of Diabetes*, **3**, 232-235.

[3] Dahlin, L.B., Güner, N., Elding Larsson, H. and Speidel, T. (2015) Vibrotactile Perception in Finger Pulps and in the Sole of the Foot in Healthy Subjects among Children or Adolescents. *PLoS ONE*, **10**, e0119753. https://doi.org/10.1371/journal.pone.0119753

[4] Alberti, K.G., Zimmet, P. and Shaw, J. (2005) IDF Epidemiology Task Force Consensus Group. The Metabolic Syndrome New Worldwide Definition. *Lancet*, **366**, 1059-1062.

[5] Margolis, D.J., Malay, D.S., Hoffstad, O.J., Leonard, C.E., MaCurdy, T., de Nava, K.L., Tan, Y., Molina, T. and Siegel, K.L. (2011) Incidence of Diabetic Foot Ulcer and Lower Extremity Amputation among Medicare Beneficiaries, 2006 to 2008. Data Points Publication Series.

[6] Shen, J., Liu, F., Zeng, H., Zhao, J.G., Zhao, W., Dong, Y. and Jia, W.P. (2009) Detection of Vibration Threshold and Its Influencing Factors in Patients with Type 2 Diabetes. *Chinese Journal Diabetes Mellitus*, **1**, 440-443.

[7] Wang, Q.S. and Yu, M. (2013) Clinical Characteristics of Type 2 Diabetes Patients with Different Risk Vibration Thresholds. *Chinese Journal Diabetes*, **21**, 149-151.

[8] Malik, R.A., Tesfaye, S., Newrick, P.G., Walker, D., Rajbhandari, S.M., Siddique, I., Sharma, A.K., Boulton, A.J., King, R.H., Thomas, P.K. and Ward, J.D. (2005) Sural

Nerve Pathology in Diabetic Patients with Minimal But Progressive Neuropathy. *Diabetologia*, **48**, 578-585. https://doi.org/10.1007/s00125-004-1663-5

[9] Elliott, J., Tesfaye, S., Chaturvedi, N., Gandhi, R.A., Stevens, L.K., Emery, C. and Fuller, J.H. (2009) Large-Fiber Dysfunction in Diabetic Peripheral Neuropathy Is Predicted by Cardiovascular Risk Factors. *Diabetes Care*, **32**, 1896-1900. https://doi.org/10.2337/dc09-0554

[10] Chong, P.S. and Cros, D.P. (2004) Technology Literature Review: Quantitative Sensory Testing. *Muscle Nerve*, **29**, 734-747. https://doi.org/10.1002/mus.20053

[11] Jia, W., Shen, Q., Bao, Y.Q., Lu, J.X., Li, M. and Xiang, K.S. (2006) Detection of Diabetic Peripheral Neuropathy and Evaluation of Its Diagnostic Value. *National Medical Journal of China*, **86**, 2707-2710.

[12] Callaghan, B.C., Little, A.A., Feldman, E.L. and Hughes, R.A. (2012) Enhanced Glucose Control for Preventing and Treating Diabetic Neuropathy. *Cochrane Database of Systematic Reviews*, CD007543. https://doi.org/10.1002/14651858.CD007543.pub2

[13] Tabak, A.G., Herder, C., Rathmann, W., Brunner, E.J. and Kivimaki, M. (2012) Prediabetes: A High-Risk State for Diabetes Development. *The Lancet*, **379**, 2279-2290. https://doi.org/10.1016/S0140-6736(12)60283-9

[14] Katon, J.G., Reiber, G.E. and Nelson, K.M. (2013) Peripheral Neuropathy Defined by Monofilament Insensitivity and Diabetes Status: NHANES 1999-2004. *Diabetes Care*, **36**, 1604-1606. https://doi.org/10.2337/dc12-1102

[15] Arif Malik, A., Qureshi, M. and Arooj, M. (2013) Assessment of Glucose Tolerance Test to Evaluate Diabetes in First Degree Relatives of Diabetics. *Pakistan Journal of Medical and Health Sciences*, **7**, 976-978.

[16] Zhang, Y., Luk, A.O.Y., Chow, E., Ko, G.T.C., Chan, M.H.M., Ng, M., Kong, A.P.S., Ma, R.C.W., Ozaki, R., So, W.Y., Chow, C.C. and Chan, J.C.N. (2017) High Risk of Conversion to Diabetes in First-Degree Relatives of Individuals with Young-Onset Type 2 Diabetes: A 12-Year Follow-up Analysis. *Diabetic Medicine*, **34**, 1701-1709. https://doi.org/10.1111/dme.13516

[17] Hu, X., He, X., Ma, X., Su, H., Ying, L., Peng, J., Wang, Y., Bao, Y., Zhou, J. and Jia, W. (2018) A Decrease in Serum 1,5-Anhydroglucitol Levels Is Associated with the Presence of a First-Degree Family History of Diabetes in a Chinese Population with Normal Glucose Tolerance. *Diabetic Medicine*, **35**, 131-136. https://doi.org/10.1111/dme.13534

[18] Dash, D.K., Choudhury, A.K., Singh, M., Mangaraj, S., Mohanty, B.K. and Baliarsinha, A.K. (2018) Effect of Parental History of Diabetes on Markers of Inflammation, Insulin Resistance and Atherosclerosis in First Degree Relatives of Patients with Type 2 Diabetes Mellitus. *Diabetes & Metabolic Syndrome*, **12**, 285-289. https://doi.org/10.1016/j.dsx.2017.12.004

[19] Callaghan, B.C., Xia, R., Banerjee, M., de Rekeneire, N., Harris, T.B., Newman, A.B., Satterfield, S., Schwartz, A.V., Vinik, A.I., Feldman, E.L. and Strotmeyer, E.S. (2016) Metabolic Syndrome Components Are Associated with Symptomatic Polyneuropathy Independent of Glycemic Status. *Diabetes Care*, **39**, 801-807. https://doi.org/10.2337/dc16-0081

[20] Cortez, M., Singleton, J.R. and Smith, A.G. (2014) Glucose Intolerance, Metabolic Syndrome, and Neuropathy. *Handbook of Clinical Neurology*, **126**, 109-122. https://doi.org/10.1016/B978-0-444-53480-4.00009-6

[21] Lee, C.C., Perkins, B.A., Kayaniyil, S., Harris, S.B., Retnakaran, R., Gerstein, H.C., Zinman, B. and Hanley, A.J. (2015) Peripheral Neuropathy and Nerve Dysfunction

in Individuals at High Risk for Type 2 Diabetes: The PROMISE Cohort. *Diabetes Care*, **38**, 793-800. https://doi.org/10.2337/dc14-2585

[22] Shen, Q., Jia, W.P., Bao, Y., Lu, J.X., Lu, H.J., Zuo, Y.H., Du, Y., Wu, X.L., Gu, H.L. and Xiang, K.S. (2009) Peripheral Neuropathy in Subjects with Diabetes Mellitus and Impaired Glucose Regulation in 2 Shanghai Communities: A Cross-Sectional Study. *Shanghai Medical Journal*, **32**, 374-378.

[23] Chen, X.Q., Bi, Y., Hu, Y., Tong, G.Y. and Zhu, D.L. (2011) Prevalence and Risk Factors of Diabetic Peripheral Neuropathy. *Journal of Medical Postgraduate*, **24**, 1035-1038.

[24] El Boghdady, N.A. and Badr, G.A. (2012) Evaluation of Oxidative Stress Markers and Vascular Risk Factors in Patients with Diabetic Peripheral Neuropathy. *Cell Biochemistry and Function*, **30**, 328-334. https://doi.org/10.1002/cbf.2808

[25] Brownlee, M. (2005) The Pathobiology of Diabetic Complications: A Unifying Mechanism. *Diabetes*, **54**, 1615-1625. https://doi.org/10.2337/diabetes.54.6.1615

[26] Groover, A.L., Ryals, J.M., Guilford, B.L., Wilson, N.M., Christianson, J.A. and Wright, D.E. (2013) Exercise-Mediated Improvements in Painful Neuropathy Associated with Prediabetes in Mice. *Pain*, **154**, 2658-2667. https://doi.org/10.1016/j.pain.2013.07.052