Research Article

TNF-Alpha in Peripheral Neuropathy Patients with Impaired Glucose Regulation

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Impaired glucose regulation (IGR) is the prestate of diabetes; about 1/3 of IGR patients will develop to diabetes finally. In this study, we investigated the serum tumor necrosis factor-alpha (TNF-α) and interleukin-6 (IL-6) levels in peripheral neuropathy impaired patients with impaired glucose regulation (IGR). A total of 70 IGR patients received the conventional nerve conduction test, including 30 patients with peripheral neuropathy (PN) and 40 patients without peripheral neuropathy (NPN). The other 40 healthy individuals were recruited as controls. The serum TNF-α and IL-6 in IGR patients were higher than in control group, and serum TNF-α and IL-6 levels in IGR-PN group were higher than in IGR-NPN group (27.7 ± 17.8 versus 13.1 ± 6.7 pg/mL and 18.1 ± 17.7 versus 6.4 ± 3.7 pg/mL, resp., both $p < 0.05$). Multifactors logistic regression analysis showed that TNF-α (OR = 0.893; $p = 0.009$) was an independent factor affecting whether IGR could combine with peripheral neuropathy. TNF-α and IL-6 could aggregate peripheral neuropathy in impaired glucose regulation patients; TNF-α might be independent risk factor for peripheral neuropathy in glucose regulation impaired patients.

1. Introduction

Abnormal glucose metabolism is one of the important reasons for the occurrence of peripheral neuropathy [1, 2]. Some patients have symptoms of peripheral neuropathy before the diagnosis of their diabetes [3]. Most impaired glucose regulation (IGR) patients will eventually develop to diabetes and the relationship between IGR and peripheral neuropathy is still controversial [4, 5]. Divisova et al. indicated that prediabetes and early type 2 diabetes mellitus are the significant risk factors of peripheral neuropathy [6]. Recently, a study showed that, based on the clinical symptoms results, 22% of diabetic patients and 23.9% of patients with abnormal glucose regulation of patients present distal symmetric multiple peripheral neuropathy [7]. These studies indicated that there were a large number of patients with diabetes and impaired glucose regulation who have peripheral neuropathy needed for early detection and intervention.

The mechanism of peripheral neuropathy has not yet been elucidated clearly. Compelling researches have indicated that the proinflammatory cytokines play important roles in the process of diabetic peripheral neuropathy. The proinflammatory cytokines such as tumor necrosis factor-alpha (TNF-α) and interleukin-6 (IL-6) participate in the process of diabetic peripheral neuropathy [8]. The recent meta-analysis showed that type 2 diabetic patients with peripheral neuropathy have obviously increased serum TNF-α levels compared to type 2 diabetic patients without peripheral neuropathy and healthy controls, and high level of serum TNF-α may be associated with increased risk of peripheral neuropathy independently [9]. Tiftikcioglu et al. showed an increase in IL-6 in those with IGT-PN [10]. In this study, we measured serum level of TNF-α and IL-6 in normal control (NC) and IGR patients with or without peripheral neuropathy to explore the mechanism of TNF-α and IL-6 in the process of peripheral neuropathy.

2. Patients and Methods

2.1. Patients and Ethnic Consideration. The study was approved and registered in the hospital ethics committee of the Tianjin Third Central Hospital in January 2014; the ethics committee approved relating screening, treatment, and data collection of these patients; all subjects signed written informed consent form. All works were undertaken following the provisions of the Declaration of Helsinki.

IGR patients were recruited from department of endocrinology and department of neurology. IGR was diagnosed according to the glucose regulation criteria of WHO in 1999 [11]. IGR includes impaired fasting glucose (IFG) and impaired glucose tolerance (IGT). 75 g oral glucose tolerance test (OGTT) was recommended for each patient; fasting plasma glucose (FPG) levels > 126 mg/dL constitute diabetes, whereas an intermediate designation IFG was established for FPG > 110 mg/dL but <126 mg/dL. A glucose level > 140 mg/dL but <200 mg/dL 2 h after a 75 g OGTT was defined as IGT. The peripheral neuropathy was diagnosed according to the criteria of American Diabetes Association (ADA) in 2010 [12]; the clinical symptoms and signs and nerve conduction abnormalities in IGR-PN group were in accordance with the diagnosis of distal symmetrical polyneuropathy. A total of 70 IGR patients were consecutively enrolled into the study.

Patients with the following criteria were excluded: (1) patients with type 1 diabetes; (2) patients with serious liver or renal insufficiency; (3) patients with severe thyroid function; (4) patients with refractory hypertension; (5) pregnant patients; (6) patients with recent history of infection; (7) patients with cerebral vascular disease; (8) patients with history of spinal joint disease; (9) patients with toxic peripheral neuritis; (10) patients with infection of multiple neuritis; (11) patients with chronic alcoholism; (12) patients with vasculitis (13); patients with autoimmune disease; (14) patients with tumors; and (15) patients who have other diagnosed nondiabetic peripheral nerve lesions.

At the meantime, another 40 healthy volunteers were recruited from the hospital's physical examination center; all of them were conformed to normal oral glucose tolerance test (OGTT) results.

2.2. Demographic Data. The demographic data including height, weight, waist circumference, body mass index (BMI), and blood pressure were recorded in the 3 groups. 12 hours after fasting, their middle elbow vein blood was drawn. The blood glucose oxidase method was used for determination of fasting blood glucose (FBG). The high pressure liquid chromatography (HPLC) method was used for determination of their glycosylated hemoglobin (HbA1c). The enzyme chemical method was used for determination of triglycerides (TG), total cholesterol (TC), high-density lipoprotein cholesterol (HDL-C), and low-density lipoprotein cholesterol (LDL-C). The powder color turbidity method was used to measure high-sensitivity C-reactive protein (hs-CRP). Their serum TNF-α and IL-6 levels were measured by chemiluminescence method (DPC1000, Siemens Healthcare Global, Erlangen, Germany).

2.3. 75 g-OGTT Methods. All subjects have been fasting since 10:00 pm before the test. Fasting blood sample was collected by venipuncture. Subjects were given 200 mL water equivalent with 75 g anhydrous glucose. They consumed the glucose load within 5 minutes. Time of subjects finishing the glucose load was recorded on the fasting blood sample tube and on the clinical chemistry form as time 0. Blood sample was taken at +120 minutes. Subjects were seated and remained within the department throughout test. Smoking and drinking tea or coffee were avoided. Prior to the OGTT of all of the subjects, restricted diet containing >150 g carbohydrate per day for 3 days was performed.

2.4. Conventional Nerve Conduction Detection. The motor conduction of median nerve, ulnar nerve, and common peroneal nerve (CPN) and the sensory conduction of median nerve, ulnar nerve, posterior tibial nerve (PTN), and sural nerve of all subjects were measured by the Dantec Keypoint Workstation (Suite, CA, USA). According to the revised criteria of Dyck et al. in 2011 [13], abnormal nerve conduction studies (NCS) were defined as one of the following criteria: prolonged incubation period; slowing of conduction velocity; reducing of CMAP and SNAP amplitude; or unsuccessful eliciting of certain arbitrary waveform.

2.5. Severity of Neuropathy. The severity of neuropathy was graded according to Toronto Clinical Scoring System (TCSS) [14]: 1–5 points for no neuropathy; 6–8 points for mild neuropathy; 9–11 points for moderate neuropathy; and 12–19 points for severe neuropathy. Symptom, reflex, and sensory tests, including pinprick, temperature, light touch, vibration, and position sensation, were performed as part of the TCSS.

2.6. Data Analysis. SPSS 18.0 software was used for analysis. Measurement data were expressed as mean ± SD and compared with single-factor variance analysis; normal distributed measurement data were compared using t-test; variance of abnormal distributed data comparison was performed according to Dunnett's analysis; chi-square test was used for count data comparison. Correlation between variables was decided by Pearson's correlation analysis and logistic regression analysis was used for multivariate analysis.

3. Results

3.1. Demographic Data Comparison. There was no statistical difference ($p > 0.05$) in age and gender distribution between 3 groups (Table 1). BMI, systolic blood pressure, and diastolic blood pressure have no statistical difference ($p > 0.05$) between IGR-PN group and IGR-NPN group, while the waistline in IGR-PN group was significantly greater than that in IGR-NPN group ($p < 0.05$).

3.2. Laboratory Parameter Comparison. As we can see from Tables 2 and 3, compared with normal control group, the FBG, OGTT-2 h glucose, HbA1c, TG, IL-6, and TNF-α in IGR-PN group and IGR-NPN group were significantly increased ($p < 0.05$). The TC level in the IGR-NPN group was

TABLE 1: Demographic data comparison in 3 groups.

	Normal control	IGR-NPN	IGR-PN
Case number	40	40	30
Gender (M/F)	20/20	20/20	15/15
Age (yr)	58.9 ± 8.6	57.7 ± 9.2	59.8 ± 10.4
BMI (kg/m^2)	22.7 ± 1.2	24.8 ± 3.4	25.7 ± 3.9
Waistline (cm)	68.6 ± 6.8	86.3 ± 8.4*	88.9 ± 10.9*,#
Systolic pressure (mmHg)	122.1 ± 8.6	132.4 ± 14.4	133.5 ± 13.3
Diastolic pressure (mmHg)	72.2 ± 7.2	82.4 ± 9.0	84.7 ± 11.6

*$p < 0.05$, compared with normal control; #$p < 0.05$, compared with IGR-NPN group.

TABLE 2: Laboratory parameter comparison in 3 groups.

	Normal control	IGR-NPN	IGR-PN
FBG (mmol/L)	5.4 ± 0.3	6.2 ± 0.8*	6.2 ± 0.9*
OGTT-2 h glucose (mmol/L)	6.5 ± 0.7	9.3 ± 1.3*	8.9 ± 1.9*
HbA1c (%)	5.2 ± 0.5	6.2 ± 0.5*	6.2 ± 0.3*
TG (mmol/L)	1.1 ± 0.3	1.6 ± 1.3*	1.7 ± 0.9*
TC (mmol/L)	4.7 ± 0.3	5.2 ± 1.1*	5.0 ± 0.9
HDL (mmol/L)	1.3 ± 0.1	1.3 ± 0.3	1.3 ± 0.2
LDL (mmol/L)	2.8 ± 0.2	3.0 ± 0.7	2.8 ± 0.6

*$p < 0.05$, compared with normal control.

TABLE 3: IL-6 and TNF-α levels in each group.

	Normal control	IGR-NPN	IGR-PN
IL-6 (pg/mL)	2.7 ± 1.0	6.4 ± 3.7*	18.1 ± 17.7*,#
TNF-α (pg/mL)	4.2 ± 1.5	13.1 ± 6.7*	27.7 ± 17.8*,#
CRP (mmol/L)	3.1 ± 1.4	3.0 ± 1.7	4.3 ± 4.7

*$p < 0.05$, compared with normal control; #$p < 0.05$, compared with IGR-NPN group.

TABLE 4: Neuropathy score comparison in 3 groups.

	Normal control	IGR-NPN	IGR-PN
Case number	40	40	30
Symptom scores	0.05 ± 0.22	0.05 ± 0.22	0.33 ± 0.48#
Reflex scores	0.18 ± 0.45	0.68 ± 0.76*	5.03 ± 1.27*,#
Sensory scores	0.30 ± 0.60	0.78 ± 0.73*	2.83 ± 1.29*,#
TCSS (score)	0.52 ± 1.01	1.52 ± 1.38*	8.01 ± 2.40*,#

*$p < 0.05$, compared with normal control; #$p < 0.05$, compared with IGR-NPN group.

TABLE 5: Nerve conduction velocity in patients with impaired glucose regulation.

NCV (m/s)	IGR-NPN	IGR-PN	p
Motor			
Median	57.90 ± 4.06	57.98 ± 4.67	0.941
Ulnar	68.97 ± 7.48	67.42 ± 6.86	0.376
CPN	49.67 ± 4.64	47.37 ± 4.78	0.046*
Sensory			
Median	49.21 ± 8.94	47.08 ± 8.39	0.315
Ulnar	57.90 ± 6.05	55.94 ± 6.94	0.213
PTN	47.60 ± 7.56	40.57 ± 6.06	0.010*
Sural	56.35 ± 5.76	53.88 ± 6.89	0.107

*$p < 0.05$ is significant.

TABLE 6: Correlation of TNF-α with nerve conduction velocity in patients with IGR-PN.

Nerve conduction velocity	r	p
Motor		
Median	−0.266	0.155
Ulnar	−0.322	0.125
CPN	−0.195	0.301
Sensory		
Median	−0.330	0.075
Ulnar	−0.244	0.194
PTN	−0.144	0.448
Sural	−0.291	0.015*

r is Pearson's coefficient. *$p < 0.05$ is significant.

significantly higher than in the NC group ($p < 0.05$), while there was no significant difference compared with the IGR-PN ($p > 0.05$). There was no statistical difference ($p > 0.05$) in HDL-C and LDL-C distribution between 3 groups ($p > 0.05$). There were no statistical differences in FBG, OGTT-2 h glucose, HbA1c, and TG between IGR-PN group and IGR-NPN group ($p > 0.05$); but IL-6 and TNF-α levels in IGR-PN group were significantly higher than those in IGR-NPN group ($p < 0.05$). The level of CRP in IGR-PN group was higher than that in the NC group and IGR-NPN group in this study, but there was no statistical difference between IGR-PN group and IGR-NPN group ($p > 0.05$), which might be caused by insufficient sample size.

3.3. Neuropathy Comparison. Nerve conduction velocities in IGR-PN group were compared with IGR-NPN group in Table 5. Motor nerve conduction velocities (MNCV) in common peroneal nerve and sensory nerve conduction velocities (SNCV) in posterior tibial nerve were significantly decreased ($p < 0.05$), while all other nerve velocities difference were not significant. Amplitudes in IGR-PN group were compared with IGR-NPN group in Table 7. CMAP amplitude in common peroneal nerve and SNAP amplitude in median nerve and posterior tibial nerve were significantly decreased ($p < 0.05$), while all other nerve amplitudes differences were not significant. Correlation of biomarker TNF-α with nerve conduction studies in IGR-PN group showed significant negative correlation with sural SNCV (Table 6) and posterior tibial nerve SNAP amplitude (Table 8).

The neuropathy scores in IGR-PN group and IGR-NPN group were significantly higher than in normal control group ($p < 0.05$, Table 4). Further comparison demonstrated that the neuropathy scores in IGR-PN group were significantly

Table 7: Nerve amplitude in patients with impaired glucose regulation.

Amplitude	IGR-NPN	IGR-PN	p
CMAP amplitude (mV)			
Median	10.48 ± 2.22	9.86 ± 2.51	0.281
Ulnar	10.18 ± 1.47	10.09 ± 1.67	0.810
CPN	5.54 ± 1.62	4.42 ± 1.51	0.004*
SNAP amplitude (μV)			
Median	19.89 ± 9.07	15.17 ± 7.48	0.023*
Ulnar	9.855 ± 3.29	8.55 ± 3.52	0.115
PTN	1.89 ± 0.97	1.29 ± 0.67	0.005*
Sural	10.05 ± 1.66	9.56 ± 1.65	0.223

*$p < 0.05$ is significant.

Table 8: Correlation of TNF-α with nerve amplitude in patients with IGR-PN.

Amplitude	r	p
CMAP amplitude (mV)		
Median	-0.074	0.544
Ulnar	-0.063	0.607
CPN	-0.036	0.769
SNAP amplitude (μV)		
Median	-0.148	0.222
Ulnar	-0.213	0.077
PTN	-0.288	0.016*
Sural	-0.016	0.934

r is Pearson's coefficient. *$p < 0.05$ is significant.

higher than those in IGR-NPN group with significant difference ($p < 0.05$).

3.4. Correlation Analysis. In this study, whether impaired glucose regulation combined with peripheral neuropathy was considered as the dependent variable or the FBG, OGTT-2 h glucose, HbA1c, TG, TC, HDL-C, LDL-C, CRP, IL-6, and TNF-α were considered as the independent variable for logistic regression analysis, the results showed that TNF-α (OR = 0.893; $p = 0.009$) was independent factor affecting whether impaired glucose regulation patient could have peripheral neuropathy. Further, Pearson's correlation analysis showed that TNF-α levels significantly positively related with TCSS score ($r = 0.331$; $p = 0.005$) (Figure 1).

4. Discussions

Abnormal glucose metabolism is the most common cause of peripheral neuropathy. Compelling studies have confirmed that immune factors are involved in the occurrence of diabetic peripheral neuropathy [15–17] and immune cytokines play important role in this process. However, the pathogenesis of impaired glucose regulation combined with peripheral neuropathy is not clear. In this study, we found that the serum levels of TNF-α and IL-6 in impaired glucose regulation (IGR) patients with peripheral neuropathy increased
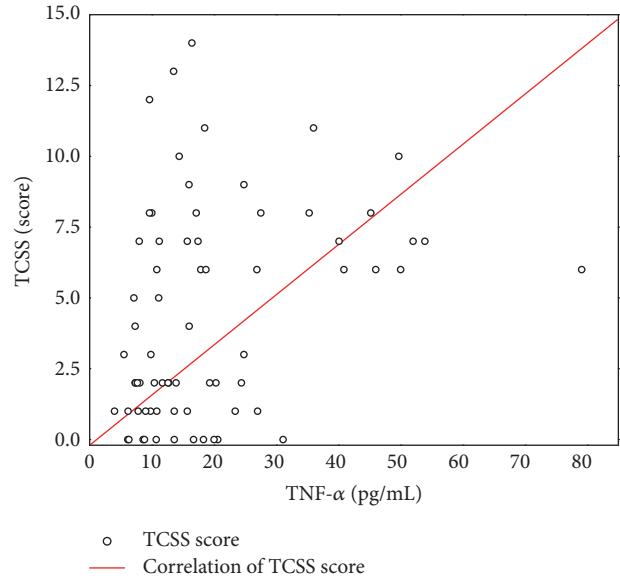

Figure 1: The correlation of TCSS score and TNF-α in IGR patients. $r = 0.331$; $p = 0.005$.

obviously, and Pearson's correlation analysis confirmed that TNF-α and TCSS were significantly positively correlated with whether IGR patients could have peripheral neuropathy. Our research suggested that immune factors, especially TNF-α, are involved with IGR peripheral neuropathy pathogenesis. In the present study, level of TNF-α in IGR-PN is correlated with sensory nerve. This result is supported by previous study, where significant correlation of TNF-α with sensory nerve conduction velocity was shown [18]. This finding also coincides with result reported by Sumner et al. and Drory et al., where it was shown that nerve function may be affected by this cytokine level [19, 20].

TNF-α is a bioactive factor activated by monocytes/macrophages, natural killer (NK) cells, B cells, and fat cells [21, 22]. The long-term hyperglycemia could cause nerve myelin protein glycosylation, which was recognized by specific macrophage later. And then the glycosylated myelin protein was phagocytosed by the macrophage. This may cause the nerve demyelination and myelin antigens to be exposed. Activated by these antigens, T cells produce a series of cytokines (including TNF-α) which raised the autoimmune response and mediated inflammatory reaction [23]. TNF-α involvement in the regulation of chronic inflammation, immune response, and multiple metabolic disorders promote the proliferation of T cells to stimulate cytokine production [24]. In addition, TNF-α has toxic effects on oligodendrocytes, can cause demyelination, and could stimulate mononuclear cells and endothelial cells secreting cytokines such as IL-1β and IL-6 and thus enhance the amplification effect of itself directly or indirectly [25].

In addition, TNF-α could inhibit endothelial nitric oxide synthase (NOS) activity, reduce the vasodilation effect induced by NO, and promote the expression of a variety of growth factors and cell adhesion molecules and thus causes

endothelial dysfunction and lead to thickening of the capillary basement membrane, swelling, hyperplasia, and hyaline degeneration of endothelial cell and finally causes the luminal stenosis, hemodynamic abnormalities, hypoperfusion, and damaging the nerve and its nutrient vessels [26].

A research performed by Yamakawa et al. demonstrated that after knocking out the TNF-α gene, the diabetic peripheral neuropathy was not developed in mice. The disappearance of TNF-α gene to completely prevent the nerve lesions of STZ induced diabetic mouse. In addition, inactivating the expression of monoclonal antibodies of TNF-α and inhibiting the expression of mRNA could play a role in the treatment of diabetic peripheral neuropathy [27]. Other studies have also demonstrated that TNF-α is important inflammatory cytokine in the treatment of diabetic peripheral neuropathy [28, 29]. Studies have also shown that serum TNF-α mediates IGT associated insulin resistance; the serum TNF-α levels in IGT patients were significantly increased and were positively related with waist circumference, high-density lipoprotein, and triglycerides [30].

TCSS is a synthesis grading system formulated based on the characteristics of DPN with advantage of being simple and comprehensive (including evaluating the symptoms and signs of subject). TCSS is suitable for large-scale epidemiological survey and evaluation of DPN severity in clinical practice. Studies have reported that the TCSS score had a moderate consistency with the nerve conduction velocity (NCV); the correlation between TCSS grading of neuropathy and NCV was better [31]. In consistency with Katulanda's result, our study shows that TNF-α levels have a significant positive correlation with TCSS, and TNF-α is an independent risk factor for peripheral neuropathy in impaired glucose regulation patients.

5. Conclusion

In conclusion, TNF-α is an independent risk factor of peripheral neuropathy in IGR patients besides hyperglycemia, blood pressure, and lipid. It may have potential clinical value in the prediction of early diabetic peripheral neuropathy. So far, there is still lack of early and effective diagnosis method for prediabetes peripheral nerve lesions in clinical practice, and prediabetic peripheral neuropathy clinical trials also lack a sensitive indicator for early detection. We hope that further basic and clinical research could provide an objective basis for early diagnosis of prediabetes peripheral neuropathy through the detection of serum TNF-α level so as to conduct the early prevention and treatment of peripheral neuropathy complications.

Competing Interests

The authors declare that there are no competing interests.

Acknowledgments

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