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Impact of impaired glucose regulation on the functions of large and small fibers of peripheral nerves

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Background/aim: This article analyzes the incidence and characteristics of peripheral neuropathy in patients with impaired glucose regulation (IGR).

Materials and methods: A total of 120 IGR patients and 60 healthy controls were enrolled. All subjects underwent nerve conduction study (NCS) of large fibers and skin sympathetic response (SSR) and contact heat pain evoked potential (CHEP) testing of small fibers with a Medtronic Keypoint machine (Medoc Ltd., Israel). IGR patients were evaluated using the Michigan Neuropathy Screening Instrument (MNSI).

Results: The abnormal rates (MNSI >2) in IGR patients and NCS and SSR evaluations were 18.3%, 22.5%, and 39.2%, respectively. All abnormal NCS findings were accompanied with abnormal SSR findings. Compared with the control group, the sensory nerve action potential wave of the posterior tibial and sural nerve was decreased in the IGR group (P = 0.01, P = 0.00), the SSR wave was reduced in the upper and lower limbs (P = 0.002, P = 0.00), and the CHEP wave was decreased in opisthenar and shank (P = 0.00). Compared with the control group, the CHEP wave was decreased in the shank in the normal SSR group (P < 0.05) and in the opisthenar and shank in the normal NCS group (P < 0.05).

Conclusion: IGR patients have peripheral neuropathy characterized by impaired functions of large and small fibers focused on small fiber and lower limb sensory nerves. CHEP can detect small fiber damage earlier than SSR and NCS.

Key words: Impaired glucose regulation, peripheral neuropathy, nerve conduction, skin sympathetic response, contact heat evoked potential

1. Introduction
Impaired glucose regulation (IGR), also known as prediabetes, is defined as the intermediate stage that is higher than the normal value of blood glucose but lower than the diabetes threshold. IGR consists of impaired fasting glucose (IFG) and impaired glucose tolerance (IGT), and 5%–10% IGR patients may develop diabetes mellitus (DM) per year. According to a report by the International Diabetes Federation, it is predicted that the number of global IGR patients will reach 471 million by 2035 (1). In China, the IGR population reached 148.2 million in 2010 (2). Peripheral neuropathy (PN) is one of the three most prevalent complications of DM and 10% of patients diagnosed with DM had accompanying PN (3). Hence, there is a growing concern about the relation between PN and IGR. At present, several researchers have already demonstrated that IGT patients have peripheral nerve lesions (4) and most of those studies were carried out with the use of clinical neurologic score and neuroelectrophysiological technologies.

In this study, we endeavor to analyze PN and its characteristics using nerve conduction study (NCS) to evaluate large fiber functions and skin sympathetic response (SSR) and contact heat pain evoked potential (CHEP) to evaluate small fiber functions. We hypothesized that IGR patients have peripheral nerve lesions, which may focus on small fibers, and that CHEP can detect small fiber lesions earlier than SSR and NCS.

2. Materials and methods
2.1. Patients
According to the IGR diagnostic criteria recommended by the World Health Organization in 2006 (5), 120 diagnosed IGR patients admitted to our hospital from January 2015 to
December 2016 were enrolled in this study. Among them, there were 56 males and 64 females aged 35–81 (58.2 ± 8.2) years. Subjects were considered to have IFG if the fasting plasma glucose was between 6.1 and 6.9 mmol/L and the 2-h oral glucose tolerance test (OGTT) was less than 7.8 mmol/L, and subjects were considered to have IGT if fasting blood glucose was less than 7.0 mmol/L and the 2-h OGTT was between 7.8 and 11.0 mmol/L.

Patients with the following diseases were excluded from the study: 1) history of ischemic and hemorrhagic cerebral vascular diseases; 2) cervical and lumbar disease (nerve root compression, spinal stenosis, degeneration of neck and lumbar spine); 3) toxic, infectious, nutritional, or immune-mediated peripheral neuropathy; 4) severe arteriovenous vascular disease (including venous thrombosis and lymphangitis); 5) neuropathy induced by toxic metabolites caused by renal failure; 6) ulcers, infections, and edema of the foot; 7) single neuropathy such as carpel and cubital tunnel syndrome; 8) other diagnosed nondiabetic peripheral neuropathies.

Sixty healthy volunteers were selected as the control group, including 28 males and 32 females aged 43–80 years (59.9 ± 7.0).

This study was approved by the Tianjin Third Central Hospital Ethics Committee, and all subjects acknowledged the burden of the intervention and provided informed consent.

2.2. Methods
Subjects lay supine in a quiet room with eyes closed at room temperature of about 22–25 °C. NCS was performed on the median nerve, ulnar nerve, posterior tibial nerve, peroneal nerve, and sural nerve; SSR on the limbs; and CHEP on the unilateral opisthenar and shank using a Medtronic Keypoint machine (Medoc Ltd., Israel).

Participants from both groups were randomly assigned numbers in the examinations and the data were collected by two neurologists without knowing the patient information.

2.3. Sports conduction
Saddle-shaped electrodes were used for stimulation and the surface electrode values were recorded. Measured parameters included complex muscle action potential (CMAP) wave and motor conduction velocity (MCV).

2.4. Sensory conduction
Ring electrode stimulation was performed and the saddle-shaped electrode value was recorded by orthodromic method. Measured parameters included sensory conduction velocity (SCV) and sensory nerve action potential (SNAP) from the median nerve of finger 1–wrist, ulnar nerve of finger 5–wrist, posterior tibial nerve of toe 1–malleolus medialis, and sural nerve ankle–lower 1/3 on the lateral shank.

2.5. SSR
Saddle-shaped electrodes stimulated the median nerve of the unilateral wrist with 50 mA for 0.2 ms. Electrodes from the centers of the palms and soles on both sides were recorded. Electrodes from the dorsal hand and sole served as references. Measured parameters included latency and amplitude. Detailed methods and normal values of NCS and SSR results have been previously discussed (6,7).

2.6. CHEP
A single pulse consecutively stimulated the unilateral dorsum of the hand and the lateral skin of the shank 5 times with a basic temperature of 32 °C and peak temperature of 51 °C by the use of a PATHWAY pain and sensory evaluation system (Medoc Ltd.). According to the standard 10-20 system, midline electrodes (Cz point) of a 64-channel surface recording cap were recorded, and the electrodes from the FPz point with impedance of less than 5 kΩ served as references. Measured parameters included N wave latency (from the start of stimulation to the start of the negative wave; data presented as ms) and N-P wave (the peak value from the max negative wave to the max positive wave; data presented as µV). Detailed methodology and instrument settings were mentioned in a previous study (8).

2.7. Michigan Neuropathy Screening Instrument (MNSI)
The MNSI was scored by the same neurologist regarding foot appearance, ankle reflex, and large toe vibration. MNSI values >2 are considered abnormal.

2.8. Statistical analysis
SPSS 20.0 (IBM Corp., Armonk, NY, USA) was used for statistical analysis and data were presented as mean ± standard deviation. Comparisons between two groups used the t-test, comparison among three groups used ANOVA, and comparison between groups used the LSD test. P < 0.05 indicates statistical significance. Power analysis was performed with PASS 15.0 (NCSS, Kaysville, UT, USA).

3. Results
3.1. Clinical and neural electrophysiological evaluation on IGR patients
The rates of abnormal MNSI scores (>2) in IGR, NCS, and SSR were 18.3%, 22.5%, and 39.2%, respectively. All patients with abnormal NCS results had abnormal SSR results; therefore, the PN incidence in IGR patients can be considered as 39.2%.

In the IGR group, the prevalence of decreasing or even disappearing ankle reflex was 33.3% (40/120); the prevalence of clinical symptoms including pain, numbness, and burning sensation was 16.7% (20/120); the prevalence of reduction or absence of large toe vibration was 20.8% (25/120); and the prevalence of reducing or disappearing monofilament sensation was 19.2% (23/120).
3.2. Comparison between IGR group and control group regarding NCS, SSR, and CHEP results
Compared with the control group, SNAP amplitude in the IGR group was decreased for posterior tibial nerve toe 1–ankle and sural nerve ankle–shank (1.51 ± 1.3 vs. 2.01 ± 1.5 µV, P = 0.01, power test = 1; 6.5 ± 1.9 vs. 10.5 ± 2.0 µV, P = 0.00, power test = 1, respectively), SSR amplitude was decreased for the upper and lower limbs (1463 ± 1140 vs. 2124 ± 1346 µV, P = 0.002, power test = 1; 531 ± 501 µV, power test = 1, respectively), and CHEP N-P amplitude was decreased for the opisthenar and shank (52.4 ± 12.6 vs. 63.0 ± 10.0 µV, P = 0.00, power test = 1; 29.3 ± 12.1 vs. 44.7 ± 12.5 µV, P = 0.00, power test = 1, respectively). Details are presented in Tables 1 and 2 and Figures 1 and 2.

3.3. Comparison of CHEP results for opisthenar and shank among the SSR, NCS, and control groups
According to the results of the NCS and SSR, IGR patients were divided into 4 groups: 73 in the normal SSR group (SSRN), 47 in the abnormal SSR group (SSRA), 93 in the normal NCS group (NCSN), and 27 in the abnormal NCS group. CHEP results of the four groups were compared. CHEP amplitude on the shank in the SSRN group was decreased compared with the control group (33.1 ± 18.9 vs. 44.7 ± 12.5 µV, P < 0.05, power test = 1; 52.4 ± 18.9 µV, P < 0.05, power test = 1); CHEP amplitude on opisthenar and the shank in the SSRA group declined compared with the control group (42.9 ± 16.5 vs. 63.0 ± 10.8 µV, P < 0.05, power test = 1; 25.5 ± 19.1 vs. 44.7 ± 12.5 µV, P < 0.05, power test = 1); CHEP amplitude on the opisthenar and the shank in the SSRN group was decreased compared with the control group (42.9 ± 16.5 vs. 62.0 ± 13.3 µV, P < 0.05, power test = 1; 25.5 ± 19.1 vs. 33.1 ± 18.9 µV, P < 0.05, power test = 0.99); and CHEP wave on the opisthenar and the shank in the NCSN group was decreased and the latency was extended compared with the control group (38.7 ± 13.5 vs. 52.4 ± 15.3 µV, P < 0.05, power test = 1; 44.7 ± 12.5 µV, P < 0.05, power test = 1) and the NCSN group (38.7 ± 13.5 vs. 52.4 ± 15.3 µV, P < 0.05, power test = 1).

Table 1. Results of NCS in the IGR group and control group (mean ± SD).

| Item                | GR n=120 | Control group n=60 | t/u value | P-value |
|---------------------|----------|--------------------|-----------|---------|
| Median nerve        |          |                    |           |         |
| CMAP amplitude (mV) | 10.1 ± 2.2 | 9.7 ± 2.0          | 1.70      | 0.09    |
| MCV (wrist–elbow) (m/s) | 58.9 ± 5.1 | 59.5 ± 3.4        | –1.17     | 0.24    |
| Finger 1–wrist SNAP amplitude (µV) | 22.8 ± 8.5 | 24.2 ± 8.7        | –1.03     | 0.15    |
| Finger 1–wrist SCV (m/s) | 52.2 ± 5.8 | 52.9 ± 5.6        | –1.31     | 0.19    |
| Ulnar nerve         |          |                    |           |         |
| CMAP amplitude (mV) | 10.4 ± 1.6 | 10.5 ± 1.5         | –0.62     | 0.53    |
| MCV (wrist–elbow) (m/s) | 62.0 ± 2.9 | 63.6 ± 3.7        | 0.04      | 0.97    |
| Finger 5–wrist SNAP amplitude (µV) | 10.5 ± 3.6 | 10.7 ± 3.2        | –0.38     | 0.35    |
| Finger 5–wrist SCV (m/s) | 57.8 ± 6.2 | 57.3 ± 5.5        | 0.23      | 0.81    |
| Posterior tibial nerve |          |                    |           |         |
| DML (ms)            | 3.5 ± 0.7  | 3.5 ± 0.8          | 0.23      | 0.81    |
| CMAP amplitude (mV) | 13.3 ± 4.20 | 13.5 ± 4.7        | –0.23     | 0.81    |
| Toe 1–ankle SNAP amplitude (µV) | 1.51 ± 1.3 | 2.01 ± 1.5        | –2.17     | 0.01*   |
| Toe 1–ankle SCV (m/s) | 48.4 ± 6.2 | 49.4 ± 7.8        | –1.03     | 0.30    |
| Peroneal nerve      |          |                    |           |         |
| CMAP amplitude (mV) | 5.5 ± 1.8  | 5.7 ± 1.7          | –0.86     | 0.39    |
| MCV (Ankle–small head) (m/s) | 49.2 ± 3.7 | 49.5 ± 4.6        | –0.56     | 0.57    |
| Sural nerve         |          |                    |           |         |
| Ankle–shank SNAP amplitude (µV) | 6.5 ± 1.9  | 10.5 ± 2.0        | –12.9     | 0.00*   |
| Ankle–shank SCV (m/s) | 58.6 ± 5.6 | 59.0 ± 6.2        | –0.41     | 0.68    |

*Statistical significance (P < 0.05).
Table 2. Results of SSR and CHEP in IGR group and control group (mean ± SD).

| Item                     | IGR n = 120 | Control group n = 60 | t-value | P-value |
|--------------------------|-------------|----------------------|---------|---------|
| **SSR**                  |             |                      |         |         |
| Upper limb latency (ms)  | 1385 ± 176  | 1356 ± 123           | 1.51    | 0.13    |
| Upper limb amplitude (µV)| 1463 ± 1140 | 2124 ± 1346          | -3.21   | 0.002*  |
| Lower limb latency (ms)  | 1820 ± 250  | 1891 ± 270           | -1.11   | 0.16    |
| Lower limb amplitude (µV)| 531 ± 501   | 892 ± 387            | -6.18   | 0.00*   |
| **CHEP**                 |             |                      |         |         |
| Hand back stimulation N wave latency (ms) | 342.5 ± 16.5 | 340.0 ± 17.8 | 0.66    | 0.50    |
| N-P wave amplitude (µV)  | 52.4 ± 12.6 | 63.0 ± 10.0          | 3.09    | 0.00*   |
| Calf irritation N wave latency (ms) | 447.5 ± 21.3 | 446.7 ± 12.9 | 0.19    | 0.84    |
| N-P wave amplitude (µV)  | 29.3 ± 12.1 | 44.7 ± 11.9          | 5.84    | 0.00*   |

*Statistical significance (P < 0.05).

Figure 1. CHEP results from shank simulation in the IGR group (A) and control group (B). Compared with the control group, CHEP-N wave latency was normal, but N-P wave amplitude decreased in the IGR group.
± 15.3 μV, P < 0.05, power test = 0.99; 21.9 ± 13.9 vs. 28.2 ± 14.4 μV, P < 0.05, power test = 0.87). Details are presented in Tables 3 and 4.

4. Discussion
PN is one of the most common complications of DM, and there is controversy regarding the presence of PN in IGR patients. Novella et al. conceded that PN may be related to prediabetes, which occurs in the early stage of diabetes (9). By the use of electrophysiological technologies, Kannan et al. (10) confirmed the hypothesis that peripheral nerve lesions can be detected in IGT patients. However, some scholars still doubt such correlations (11). Different detection methods may also lead to different prevalences of prediabetes. Ziegler et al. (12) detected 24.3% risk of PN in prediabetic patients with MNSI scores of >2 as
Compared with the control group and SSRN group, $P < 0.05$.

Compared with the control group, $P < 0.05$.

Table 3. Results of CHEP for opisthenar and shank in SSRA, SSRN, and control groups (mean ± SD).

| Group           | n  | Hand back stimulation | Calf irritation |
|-----------------|----|-----------------------|-----------------|
| N wave latency  | ms |                       |                 |
| SSRA group      | 47 | 342.5 ± 16.9          | 450.6 ± 22.7    |
| SSRN group      | 73 | 342.6 ± 19.8          | 444.7 ± 23.0    |
| Control group   | 60 | 340.0 ± 17.9          | 446.7 ± 12.5    |
| N-P wave amplitude (µV) |
| SSRA group      | 59 | 42.9 ± 16.5**         | 25.5 ± 19.1**   |
| SSRN group      | 61 | 62.0 ± 13.3           | 33.1 ± 18.9*    |
| Control group   | 40 | 63.0 ± 10.8           | 44.7 ± 12.5     |

*Compared with the control group, $P < 0.05$.
**Compared with the control group and SSRN group, $P < 0.05$.

Table 4. Results of CHEP for opisthenar and shank in NCSA, NCSN, and control groups (mean ± SD).

| Group           | n  | Hand back stimulation | Calf irritation |
|-----------------|----|-----------------------|-----------------|
| N wave latency  | ms |                       |                 |
| NCSA group      | 27 | 363.6 ± 24.2**        | 461.1 ± 22.7**  |
| NCSN group      | 93 | 345.5 ± 18.9          | 448.5 ± 25.7    |
| Control group   | 60 | 340.0 ± 17.9          | 446.7 ± 12.5    |
| N-P wave amplitude (µV) |
| NCSA group      | 27 | 38.7 ± 13.5**         | 21.9 ± 13.9**   |
| NCSN group      | 61 | 52.4 ± 15.3*          | 28.2 ± 14.9*    |
| Control group   | 60 | 63.0 ± 10.8           | 44.7 ± 12.5     |

*Compared with the control group, $P < 0.05$.
**Compared with the control group and NCSN group, $P < 0.05$.

the diagnostic criterion for PN. A community study in China (13) evaluated 268 IGR cases and 91 DM cases by MNSI, revealing that the PN prevalences in IGR and DM patients were 24.6% and 36.6%, respectively. In addition, more peripheral nerve damage can be detected with the application of neurophysiological technologies. Kannan et al. (10) found that the prevalence of IGT patients with PN was 32.8% by using NCS, quantitative sensory measurement (QST), and autonomic testing. In the current study, we analyzed the abnormal rate in IGR patients and the patients went through NCS and SSR tests based on MNSI scores (>2). We found that the prevalences of patients with abnormal MNSI scores (>2) were 18.3%, 22.5%, and 39.2% in the total IGR patients, the NCS group, and the SSR group. Abnormal MNSI scores (>2) were always accompanied with abnormal SSR results; therefore, we speculated that the prevalence of PN in IGR patients was 39.2%.

Then we compared the results of NCS, SSR, and CHEP between IGR patients and healthy volunteers. NCS was used to evaluate the function of large myelinated nerve fiber Aα while SSR and CHEP were used to evaluate small nerve fibers of class C and Aδ. As a result, we found that in IGR patients, SNAP amplitude decreased in the posterior tibial nerve and sural nerve, SSR amplitude decreased in the upper and lower extremities, and CHEP N-P wave amplitude decreased in the opisthenar and the shank. All these outcomes indicated that IGR patients have peripheral nerve damage focusing on the small nerve fibers and lower limb sensory fibers, with the characteristics of axon impairment and length dependence. Green et al. (14) found that lesions in IGT patients were focused on C class myelinated fibers. Isak et al. (15) detected that GT patients only had reduction of the SSR wave compared with a control group by NCS, SSR, and autonomic nerve function evaluation, which suggested that PN would appear as small fiber neuropathy at an early stage. Kannan et al. (10) evaluated peripheral nerve lesions in patients with prediabetes using NCS, autonomic function evaluation, and QST and found that prediabetic patients had lesions not only on small fibers but also on large sensory fibers, which is consistent with our results.

Finally, we compared the CHEP results of the SSRN, SSRA, NCSN, and NCSA groups based on MNSI scores and demonstrated that CHEP can detect small fiber lesions in the early phrase in IGR patients better than SSR and NCS, and lesions will become worse if the SSR and NCS evaluations deteriorate to abnormal. As a noninvasive technique detecting small fiber pathways from the skin to the cerebral cortex, CHEP can reflect the fiber function of Aδ and class C, which is also more stable and objective than SSR (16). Our previous studies (8,17) found that CHEP can detect small fiber lesions earlier in diabetic patients, as the CHEP N-P wave was decreased in forearms and shanks in the NCSN group. Wong et al. (17) found that, compared with a healthy control group, the CHEP N1-P1 wave was decreased in lateral shanks in a DM group with or without lower extremity symptoms, suggesting that N1-P1 amplitude reflecting an early stage of small fibrosis can be detected by CHEP.

However, there is still no consensus on the mechanism of peripheral nerve damage in IGR patients. Some researchers suggest that it is similar to the mechanism of diabetic neuropathy, which includes chronic hyperglycemia, dyslipidemia, microangiopathy, and metabolic syndrome (18,19). On the other hand, some studies propose that rather than increasing blood glucose, prediabetic PN is associated with abnormal insulin signal, dyslipidemia, and endoplasmic reticulum stress (20). Besides, “small fiber” refers to the unmyelinated or myelinated sensory fibers that
are susceptible to any damage, which is why the current study and previous researchers detected that peripheral nerve lesions were focused on small nerve fibers.

In summary, this study demonstrated that the prevalence of PN in IGR patients was 39.2%, that neurophysiological technologies can detect early peripheral neuropathy characterized by lesions on large and small fibers and focused on the small fibers and lower limb sensory fibers, and CHEP can detect small fiber lesions in IGR patients earlier than SSR and NCS. Therefore, we suggest that more attention be paid to preventing and treating peripheral neuropathy in the early stage of diabetes, since those lesions are relatively mild and easier to cure.

However, there are still some limitations of this study. First, SSR and CHEP can be used to evaluate class C and Aβ fibers, but they are not the best for detecting small fibers, which are susceptible to many factors. Second, intradermal nerve fiber density can serve as the golden standard for detecting small fibers, which is an invasive form of examination. However, further studies can apply this method to convey more accurate results. Third, this study only focused on the symptoms and characteristics of PN in IGR patients; therefore, further studies should pay attention to the risk factors and the mechanism of this disease.

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