Thermoregulation and Thermal Perception in Diabetic Peripheral Neuropathy: A Pathophysiological Perspective of Evaluation and Management

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Abstract

Background: Thermoregulation and thermal perception was considered as two independent processes involved with perceiving hot or cold stimuli which reflected small-fiber dysfunction in diabetic peripheral neuropathy (DPN). **Objective:** To explore and synthesize the existing evidence for thermoregulation and thermal perception for their testing and treatment methods in DPN from a pathophysiological perspective. **Methods:** A systematic review of PubMed, CINAHL and Google scholar was done using search terms "thermoregulation, thermal-hot/cold" to identify relevant citations for their inclusion after a three-level scrutiny for data extraction and descriptive synthesis into evaluation and management. **Results:** Of the total 30 included studies, 16 studies were on thermoregulation (body temperature=4, cold immersion recovery=1, warm immersion recovery=1, bronchial cold reactivity=1, cold pressor response=1, heat evoked potentials=2, thermal biofeedback=1, thermography/thermometry=3, device-specific use=2) and five studies were on thermal perception thresholds, one study on cooling detection thresholds and one study on heat pain thresholds. There were seven studies on interventions (cucumin=1, lycopene=1, quercetin=1, resveratrol=1, tapentadol=1, bone marrow transplantation=1, trolox=1). **Conclusion:** Thermoregulation and thermal sensory perception were altered in DPN, which was evidently demonstrated as changes in temperature, responses to immersion, heat evoked potentials, thermal perception thresholds, and thermal pain thresholds during assessment, and was positively reflecting therapeutic effects, efficacy and effectiveness of variety of interventions.

Keywords: Thermoregulation; Thermal sensory examination; Thermoreception; Diabetic neuropathy.

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Introduction

Pain was the first and foremost sensory perception emphasized over the years of

scientific development in the field of Medicine and healthcare.[1] In 1890s, neuroscientific observations of impaired temperature sensation together with that of pain had led to the supposition that the two sensations had a common anatomical pathway.[2]

Subsequently, thermal and non-thermal factors[3] and their role in bodily mechanisms for temperature control was gaining priority studying the influence of human circadian rhythms,[4] serotonergic system,[5] and central nervous system.[6] Then the emphasis undertook a shift from studies on thermoregulation and thermoregulatory mechanisms differentiating general and local temperature,[7] and neurophysiological evidence directed emphasis on thermal sensation as playing a vital role in health and disease.[8]

Later, the independent roles of temperature and thermal perception in the control of human thermoregulatory behavior was understood from a behavioral role of perceiving thermal sensation and thermal discomfort.[9] The importance of evaluating thermal sensation as one among the protective sensations arose from the incidence of accidental burns due to sensory deficits in hands/feet among people with peripheral nerve injuries.[10]

Anecdotally, thermal sensation was evaluated in the bedside neurological examination by touch, contact with objects and differentiating into hot/cold which were prone for huge inter-individual variability from a multifactorial viewpoint: patient-specific, therapist-specific and disease-specific.[11] Initial attempts to use visual analogue scales for quantifying self-rated thermal sensation was too subjective[12] for continuing its use for practice.

Quantitative sensory testing (QST) is objectified measurement method for evaluating sensations including touch, temperature, vibration, pressure, pain and two-point discrimination.[13,14] German Research Network on Neuropathic Pain (DFNS) had reiterated the importance of assessment of thermal sensation and thermal perception and thermal pain thresholds as part of routine QST15 for evaluation of small fiber dysfunction.[16]

"Clinically, QST may be useful for 1) the identification of subgroups of patients with different underlying pain mechanisms; 2) prediction of therapeutic outcomes; and 3) quantification of therapeutic interventions in neuropathic pain therapy."[17] In patients with primary complaints of neuropathic pain, QST can be used to determine detection, pain thresholds and stimulus-response curves and can thus detect both negative and positive sensory signs, the second ones not being assessed by other methods.[18]

Compared to regular clinical examination, QST could detect more abnormalities much earlier in the course of diabetic polyneuropathy and hence could aid as a valuable evaluation tool.[19] In diabetic peripheral neuropathy (DPN), the most intolerable symptom for patients is pain, which was not predicted by small-fiber dysfunction measured using QST. [20]

Identifying loss of protective sensation such as thermal sensation and/or thresholds on the plantar aspect of foot[21] and appropriately defining distal symmetric sensorimotor polyneuropathy[22] would enable early and appropriate delineation of high-risk or risk for ulceration[23] and lower extremity amputations[24] in feet of diabetic individuals.

Thus the objective of this study was to explore and synthesize the existing evidence for thermoregulation and thermal perception for their testing and treatment methods in DPN from a pathophysiological perspective.

Methodology

A systematic review of PubMed, CINAHL and Google scholar was done using search terms "(cold [Title] OR cooling [Title] OR temperature [Title] OR thermal [Title] OR heat [Title] OR hot [Title] OR warmth [Title] OR warm [Title]) AND (diabetes [Title] OR diabetic [Title]) AND (neuropathy [Title] OR neuropathic [Title])" to identify relevant

citations for their inclusion after a three-level scrutiny (title, abstract and full-text) for data extraction and descriptive synthesis into evaluation and management studies.

Results

Of the total 30 included studies, 16 studies were on thermoregulation (body temperature=4, cold immersion recovery=1, warm immersion recovery=1, bronchial cold reactivity=1, cold pressor response=1, heat evoked potentials=2, thermal biofeedback=1, thermography/thermometry=3, device-specific use=2) and five studies were on thermal perception thresholds, one study on cooling detection thresholds and one study on heat pain thresholds. There were seven studies on interventions (cucumin=1, lycopene=1, quercetin=1, resveratrol=1, tapentadol=1, bone marrow transplantation=1, trolox=1).

Thermoregulatory function

Body temperature

Bagavathiappan *et al*[25] assessed the correlation between plantar foot temperature and diabetic neuropathy using a non-invasive infrared thermal imaging technique in 112 subjects who had VPT > 20V and they found that DPN patients had a higher foot temperature (32-35^{0}C) compared to patients without neuropathy (27-30^{0}C). Mean foot temperature (MFT) showed a positive correlation with right and left great toe VPT values.

Naicker *et al*[26] undertook a cross-sectional study to identify risk factors for diabetic neuropathy and the association between foot temperature and development of diabetic neuropathy by studying 134 diabetic patients with peripheral neuropathy. Low foot temperature was not significantly associated with development of diabetic neuropathy which indicated that foot temperature alteration was merely an effect of autonomic neuropathy attributable to co-existing peripheral arterial disease.

Boyko *et al*[27] re-examined the association between skin temperature and autonomic neuropathy in a cross-sectional study of 712 veterans with diabetes mellitus. An infrared surface scanner was used to measure foot skin temperature at multiple sites. Subjects with sensory neuropathy had lower mean plantar foot skin temperature than those without (28.4^{0}C vs. 28.9^{0}C). Their results suggested that skin temperature might be slightly lower with higher orthostatic blood pressure fall in diabetic veterans.

Papanas *et al*[28] evaluated foot temperature in 30 type 2 diabetic patients with vs. 30 patients without peripheral neuropathy. Dorsal and plantar foot temperatures were significantly higher in group with neuropathy than in group without neuropathy.

Kitamura *et al*[29] studied 36 non-diabetic patients (control group) and 27 diabetic patients (diabetic group) undergoing elective abdominal surgery using standard non-invasive autonomic tests (heart rate variation at deep periodical breathing, Valsalva maneuver, and head-up tilt). The core temperature of the diabetic patients with autonomic dysfunction was lower from 120 min (35.1^{0}C) onward compared with the diabetic patients with normal autonomic function. The current study results indicated that diabetic autonomic neuropathy was associated with more severe intraoperative hypothermia.

Cold immersion recovery test

Bharara *et al*[30] investigated the effectiveness of testing cold immersion recovery responses in the diabetic foot with neuropathy using a contact thermography system based on thermochromic liquid crystals in 81 subjects with no history of diabetic foot ulceration who were assigned to neuropathy, non neuropathy and healthy groups. Patients with diabetes with neuropathy show the highest 'delta temperature', that is difference between the temperature after 10-minute recovery period and baseline temperature measured independently at all the three sites (first metatarsal head (MTH), second MTH and heel).

Warm immersion recovery test

Bharara *et al*[31] presented results of warm immersion recovery test in the diabetic foot with neuropathy using a liquid crystal-based contact thermography system in 81 subjects who were assigned to one of three study groups, that is diabetic neuropathy, diabetic non neuropathy and non diabetic healthy. Local measurements at the most prevalent sites of ulceration, that is metatarsal heads, great toe and heel, show highest temperature deficit after recovery for diabetic neuropathy group.

Bronchial cold reactivity

Heaton *et al*[32] compared five diabetic patients with severe symptomatic autonomic neuropathy, five diabetic patients without autonomic neuropathy and five non-diabetic controls for their responses to bronchial provocation testing with cold air. The first group did not show a significant fall in specific airways conductance, whereas conductance fell in the second group by 30.8% and in the third group by 22.7%.

Cold pressor test

Sayinalp *et al*[33] applied the cold pressor test to a group of 33 diabetic patients and 15 healthy controls. The mean diastolic cold pressor response was significantly lower in diabetic patients as compared with the control group.

Heat-evoked potentials

Chao *et al*[34] investigated the diagnostic role of Contact heat-evoked potential (CHEP) to record cerebral responses of Aδ fiber-mediated thermonociceptive stimuli in 32 type 2 diabetic patients with skin denervation and neuropathic pain. Abnormal CHEP patterns (reduced amplitude or prolonged latency) were noted in 81.3% of these patients. The CHEP amplitude was the most significant parameter correlated with IENF density and pain perception to contact heat stimuli.

Wong and Chung[35] compared contact heat evoked potential (CHEP) parameters between healthy adults and diabetics with and without lower limb symptoms and found a significant difference in N1-P1 amplitude in the three groups after stimulation of the dorsum of the foot and the point 10 cm proximal to the lateral malleolus. CHEP thus could help to detect early A-delta fiber damage in diabetic patients with minimal neuropathy.

Thermal biofeedback

Fiero *et al*[36] examined association of nerve function with four common types of diabetic neuropathy (sympathetic-autonomic, vagal-autonomic, sensory, and motor) on 24 participants with diabetes mellitus (19 with type II and 5 with type I) whose hand temperature, foot temperature, and electrodermal gradient at the toes were monitored across six thermal biofeedback sessions. Participants were able to significantly raise foot temperatures across sessions, an average of 2.2^0 F, with lower-extremity sympathetic-autonomic and sensory neuropathies interfering with foot warming.

Thermography and thermometry

Bharara *et al*[37] emphasized on applications of thermography and thermometry in lower extremity wounds, vascular complications, and neuropathic complications which had progressed as a result of improved imaging software and transducer technology. The authors reviewed thermal measurement techniques specific to diabetic foot such as electrical contact thermometry, cutaneous thermal discrimination thresholds, infrared thermography, and liquid crystal thermography.

Fushimi *et al*[38] studied the thermographic patterns of 62 patients, who demonstrated contralateral leg vasodilatatory response to warm water immersion indicative of sympathetic neuropathy, using Thermoviewer MDJTG-MD. The thermographic pattern was found to be closely related to microangiopathy, R-R interval variation and motor nerve conduction velocity, with excellent reproducibility and required simple and non-invasive techniques.

Sundkvist *et al*[39] assessed the relationship between neuropathy and peripheral circulation (thermography) in 26 patients with a short to moderate duration (less than 20 years) and in 26 patients with a long duration (more than 20 years) of diabetes mellitus. The authors found a markedly delayed toe temperature increase after cooling followed by indirect heating occurred in diabetics of short duration with autonomic neuropathy (AN).

Device-specific use

Viswanathan *et al*[40] determine the effectiveness of Tip-therm, a temperature discriminator, in making an early diagnosis of distal symmetrical polyneuropathy in 910 diabetic patients and found that Tip-therm appeared to be an inexpensive, highly sensitive, and specific device for detection of diabetic neuropathy when compared with biothesiometry and a monofilament.

Arezzo *et al*[41] reported use of Thermal Sensitivity Tester (TST) and determined its normative values of threshold for detecting the colder surface using a two-alternative, forced-choice algorithm. The mean threshold in the normal population was found to be 0.67^0C and 1.01^0C for the index finger and great toe, respectively.

Thermal perception thresholds

Løseth *et al*[42] determined if neuropathy in diabetic patients could be detected by measurements of thermal thresholds, and compared the differences in parameters between 22 patients with and 37 patients without neuropathic symptoms. Thermal thresholds were significantly elevated (more abnormal) in patients with symptoms compared to controls, but only for cold perception threshold (CPT) in the asymptomatic group. When comparing symptomatic and asymptomatic patients, there was no statistically significant difference in thermal thresholds.

Batista *et al*[43] studied 60 adult subjects (30 young healthy individuals without a history of diabetes, and 26 individuals with adult onset diabetes and four with juvenile onset). Thermal sensitivity testing was performed with custom devices fabricated from materials with different thermal conduction capacities (copper, steel, glass, and plastic). There was a strong relationship found between cold perception and stimulation with the copper probe in dermatomes of the radial nerve of the upper limb and the superficial peroneal dermatome of the lower limb. The study concluded that thermal sensitivity to copper and cold stimulation might be more discriminative and have a higher threshold than sensitivity to the Semmes-Weinstein monofilament.

Levy *et al*[44] compared the method of limits or a forced-choice method for testing TPT, cooling and heat pain thresholds in 367 diabetic patients, 128 with symptomatic neuropathy. FC thermal thresholds increase with age in normal subjects, but not to a clinically significant degree. In diabetics FC warm threshold increased by 0.8^0C/decade, ML by 0.1^0C/decade. The prevalence of abnormal thresholds was found to be similar for both methods (28-32%). Only 15-18% of patients had abnormal results in both tests.

Bertelsmann *et al*[45] investigated thermal cutaneous sensation (thermal discrimination thresholds) of the hand and the foot in 36 normal subjects and in 20 patients with diabetic neuropathy. In patients with diabetic neuropathy the increased thresholds for the foot could be correlated with length-dependent degeneration of small nerve fibres.

Guy *et al*[46] undertook sensory evaluation of thermal sensitivity in four groups of patients with diabetic neuropathy: 22 with neuropathic ulcers and/or Charcot joints (groups 1 and 2); 15 patients with painful neuropathy (group 4), 10 patients with autonomic neuropathy alone (group 3) and found that thermal testing was able to detect abnormalities in all 4 groups. Comparison of thermal sensitivity (a small fibre modality) with vibration perception threshold (a large fibre modality) showed that thermal sensitivity was sometimes selectively affected, which suggested that the small fibres are more vulnerable in diabetes.

Cooling detection thresholds

Dyck *et al*[47] evaluated neuropathic symptoms [neuropathy symptom score (NSS) and neuropathy scale of neuropathy symptom profile (NNSP)], deficits [neurologic disability score (NDS) and vibratory (VDT) and cooling (CDT) detection thresholds], or nerve dysfunction [nerve conduction (NC)] in 180 diabetics, and found that NC was abnormal in 69%, NSS in 54%, NDS in 48%, NNSP in 47%, VDT in 44%, and CDT in 35%.

Heat pain thresholds

Hilz *et al*[48] determined the parameters that predict alterations in warm, cold and heat pain threshold using a "Marstock" Thermo-stimulator in 26 diabetics and 32 healthy subjects. While heat pain determinations were not useful, determination of cold perception, at a moderate rate of temperature change, proved to be the most reliable indicator of small fiber lesions. Cold thresholds as well as their intra individual ranges were most often impaired.

Interventions

Curcumin

Sharma *et al*[49] explored the antinociceptive effect of curcumin and its effect on tumour necrosis factor-alpha (TNF-alpha) and nitric oxide (NO) release in streptozotocin induced diabetic mice and found that 4 weeks treatment with curcumin attenuated thermal hyperalgesia and the hot-plate latencies. Their study results indicated an antinociceptive activity of curcumin possibly through its inhibitory action on NO and TNF-alpha release.

Lycopene

Kuhad *et al*[50] explored the antinociceptive effect of lycopene and its effect on tumour necrosis factor-alpha (TNF-alpha) and nitric oxide (NO) release in streptozotocin induced diabetic mice which were tested in the tail immersion and hot-plate assays. Lycopene treatment significantly attenuated thermal

hyperalgesia and the hot-plate latencies.

Quercetin

Anjaneyulu and Chopra[51] explored the antinociceptive effect of a bioflavonoid, quercetin, both in control and streptozotocin (STZ)-induced diabetic mice and found that Quercetin (100 but not 50 mg/kg p.o.) produced a marked increase in tail-flick latencies of thermal (warmth) hyperalgesia in both diabetic and nondiabetic mice.

Resveratrol

Sharma *et al*[52] explored the antinociceptive effect of resveratrol on diabetic neuropathic pain in DPN rats and found that daily treatment with resveratrol for 4 weeks starting from the 4th week of STZ injection significantly attenuated thermal hyperalgesia.

Tapentadol

Christoph *et al*[53] studied effects of Tapentadol (a novel analgesic with two modes of action, mu-opioid receptor (MOR) agonism and noradrenaline (NA) reuptake inhibition) on thermal hyperalgesia in DPN mice and found that Tapentadol was more potent than morphine against heat hyperalgesia in a dose-dependent manner.

Transplantation of bone marrow-derived mononuclear cells

Naruse *et al*[54] investigated whether transplantation of freshly isolated bone marrow-derived mononuclear cells (BM-MNCs) alleviates neuropathic pain in the early stage of streptozotocin-induced diabetic rats, and found that BM-MNC transplantation significantly ameliorated mechanical hyperalgesia and cold allodynia.

Trolox

Sharma and Sayyed[55] targeted oxidative stress in DPN using trolox, an anti-oxidant, in streptozotocin-induced diabetic neuropathy in

rats and found two weeks treatment with trolox started on completion of the 6th week of diabetes significantly improved MNCV, NBF and inhibited thermal hyperalgesia.

Discussion

The objective of this study was to explore and synthesize the existing evidence for thermal perception and its testing and treatment methods in DPN from a bench-to-bedside perspective. The existing evidence although limited, provide a fairly sufficient information on role of thermal perception and its evaluation of small-fiber dysfunction in DPN which presented either positively or negatively and the therapeutic role of a myriad of management methods for ameliorating thermal hyperalgesia or allodynia.

Reliability of thermal quantitative sensory testing was variable, with the reliability of cold and warm detection thresholds ranged from poor to excellent, while heat and cold pain thresholds ranged from fair to excellent.[56] Thermal perception threshold and thermal pain threshold testing are influenced by inter-trial interval and the order of testing.[57] It is also essential to evaluate pain ratings during threshold testing in order to standardize the interpretation of QST.[58]

The use of thermal QST in people with pain raises questions proposed by Granot *et al*:[59] "(a) Are pain scores for short-term repeated phasic stimuli consistent? (b) Does an exposure to tonic heat pain stimulus cause sensitization and change the scores for subsequent phasic stimuli? and (c) Are pain scores for phasic and tonic heat pain correlated? Which were answered respectively as follows: (i) phasic pain scores assessments at 30' and 60' after baseline is consistent; (ii) tonic heat pain, despite relatively high VAS scores, does not cause a change in the scoring of subsequent phasic stimuli; and (iii) phasic and tonic pain scores correlate with each other."

Factors such as age (Lin *et al*, 2005),[60] site of testing, temperature of part,[61] skin temperature distribution,[62] stimulus (type, characteristics, quantity, presentation, testing format, and environment) but also the response (form and analysis),[63] types of instruments, [64] cutaneous mechanoreceptors,[65] determination paradigm and reference temperature[66] influence the accuracy of testing and these should be invariably kept in mind by the practicing clinician.

There were different methods of recording-method of limits[67] which can reliably detect c- and a-delta fiber-mediated thermal perception[68] which deserve comparison in people with DPN. Olney[69] provided recommendations for clinical trials on polyneuropathy using QST as outcome measures that cooling and warming detection thresholds have good sensitivity for small myelinated sensory fibers.

Recent developments such as computer-assisted sensory examination of thermal thresholds were reported to be accurate, convenient and inexpensive, where the clinical data could easily be utilized as a scientific data.[70] Such methods would enable better knowledge-practice translation of evidence-informed scientific developments.

Future assessment studies should compare the measurement properties of types and methods of thermal perception and thermal pain threshold testing for enhancing their evidence-informed use in assessment of people with DPN. Future intervention studies should study the effects of interventions on small-fiber dysfunction in DPN through thermal sensory testing methods.

Conclusion

Thermoregulation and thermal sensory perception were altered in DPN, which was evidently demonstrated as changes in temperature, responses to immersion, heat evoked potentials, thermal perception thresholds, and thermal pain thresholds during assessment, and was positively reflecting therapeutic effects, efficacy and effectiveness of variety of interventions.

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