From Mechanisms to Therapy: Post-Print of Diabetic Autonomic Neuropathy

Authors: Pan Ziyun, Yin Hao, Lin Zhirou, Mao Jingyi, Huang Yan, Luo Yanhua, Xiao Jiafu, Hu Yin, Hu Yin

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Abstract

Diabetic neuropathy (DN) is the most common and most destructive chronic complication of diabetes, among which autonomic neuropathy has attracted considerable attention due to its involvement of multiple organ system functions. Pathological mechanisms such as metabolic abnormalities, oxidative stress, and microvascular lesions triggered by hyperglycemia can lead to autonomic nervous system dysfunction, causing clinical symptoms such as resting tachycardia, gastroparesis, and bladder dysfunction. In the treatment of diabetic autonomic neuropathy (DAN), optimizing glycemic control serves as the foundation, combined with aldose reductase inhibitors, antioxidants, and neurotrophic drugs to synergistically alleviate clinical symptoms. Furthermore, through the utilization of neuromodulation techniques and implementation of individualized interventions, targeted regulation of systemic damage can be achieved. This article reviews the pathophysiological mechanisms of DAN, clinical manifestations in multiple tissues and organs, and treatment strategies based on autonomic nervous system regulation, aiming to provide a theoretical foundation for in-depth analysis of DN pathological mechanisms and optimization of clinical intervention strategies.

Full Text

From Mechanism to Therapy: Diabetic Autonomic Neuropathy

PAN Ziyun[12], **YIN Hao**[3], **LIN Zhirou**[1], **MAO Jingyi**[1], **HUANG Yan**[1], **LUO Yanhua**[1], **XIAO Jiafu**[1], **HU Yin**[1]*

[1]Department of Metabolism and Endocrinology, the First Affiliated Hospital, Hengyang Medical School, University of South China, Hengyang 421001, China
[2]Department of Laboratory Medicine, the First Affiliated Hospital, Hengyang

Medical School, University of South China, Hengyang 421001, China
[3]Department of Rehabilitation Medicine, the First Affiliated Hospital, Hengyang Medical School, University of South China, Hengyang 421001, China

Corresponding author: HU Yin, Associate professor/Master supervisor; E-mail: yinhu_{2020}@163.com

Abstract

Diabetic neuropathy (DN) represents one of the most common and devastating chronic complications of diabetes, with autonomic neuropathy attracting particular attention due to its involvement of multiple organ systems. Pathological mechanisms triggered by chronic hyperglycemia—including metabolic abnormalities, oxidative stress, and microvascular lesions—can lead to autonomic nervous system dysfunction, causing clinical manifestations such as resting tachycardia, gastroparesis, and bladder dysfunction. In the management of diabetic autonomic neuropathy (DAN), optimizing glycemic control serves as the foundation, supplemented by aldose reductase inhibitors, antioxidants, and neurotrophic agents to synergistically alleviate symptoms. Furthermore, neuromodulation techniques and individualized interventions enable targeted regulation of systemic damage. This review summarizes the pathophysiological mechanisms of DAN, its clinical manifestations across multiple tissues and organs, and therapeutic strategies based on autonomic nervous system modulation, aiming to provide a theoretical basis for in-depth analysis of DN pathogenesis and optimization of clinical intervention strategies.

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Diabetic neuropathy (DN) is among the most common chronic complications of diabetes, with undeniable clinical significance. As diabetes progresses, approximately half of all patients eventually develop some form of neuropathy. DN is a heterogeneous syndrome of nervous system damage induced by chronic hyperglycemia and its metabolic disturbances, with diverse clinical presentations. It can be classified into three major categories: diffuse neuropathy, mononeuropathy, and radiculoplexus neuropathy. The former includes distal symmetric polyneuropathy (DSPN) and DAN, with DSPN being the most prevalent, accounting for about 75% of all DN cases. Autonomic neuropathy is the second most common form, broadly referring to autonomic nerve damage involving the cardiovascular, gastrointestinal, and urogenital systems. Mononeuropathy is relatively common due to local microvascular ischemia or compressive trauma. Notably, DSPN and autonomic neuropathy frequently coexist, and small-fiber neuropathy often involves both sensory impairment and autonomic fiber dam-

age, causing patients to experience sensory abnormalities accompanied by reduced sweating and other autonomic changes [**?**]. Research indicates that DAN is closely related to patient prognosis; for instance, severe cardiovascular autonomic neuropathy can result in a 5-year mortality rate as high as 25–50%, significantly higher than in those without this complication [**?**].

Because the autonomic nervous system (ANS) is widely distributed throughout the body, all organs are susceptible to autonomic dysfunction in diabetes. Recent advances in research have led to continuous updates in international guidelines, offering new insights into the classification, diagnosis, and treatment of DN [**?**]. The ANS, composed of the sympathetic, parasympathetic, and enteric nervous systems, plays a central role in maintaining homeostasis by regulating unconscious functions such as heart rate, blood pressure, gastrointestinal motility, sweating, and body temperature [**?**]. Diabetic autonomic neuropathy (DAN), an important subtype of DN, often causes resting tachycardia, gastroparesis, urinary difficulties, abnormal sweating, and foot ulcers, severely impacting patients' quality of life and prognosis [**?**]. Therefore, exploring the mechanisms and treatment of DAN in the context of diabetes is of great significance, as diabetes-induced autonomic dysfunction directly leads to multi-system imbalance and damage. This review examines the mechanisms of DAN in various tissues and organs, its clinical manifestations, and DN treatment strategies based on ANS modulation (Figure 1 [Figure 1: see original paper]), aiming to provide insights into DN pathogenesis and new directions for clinical research.

Pathophysiological Mechanisms of DAN

In diabetes, persistent hyperglycemia activates multiple interconnected metabolic pathways that collectively mediate nerve tissue damage. The primary mechanisms include: excessive activation of the polyol pathway leading to sorbitol accumulation and oxidative stress; promotion of advanced glycation end product (AGE) formation and activation of downstream receptor signaling; abnormal activation of protein kinase C pathways that directly disrupt nerve cell structure and function [**?**]; and activation of the hexosamine pathway, whose end products mediate abnormal protein modifications that interfere with normal signal transduction. Microvascular lesions further exacerbate damage, manifesting as endothelial dysfunction of vasa nervorum, basement membrane thickening, and neurotissue ischemia/hypoxia due to imbalance of vasomotor factors [**?**]. The hyperglycemic environment also induces systemic insulin resistance and inflammatory responses, stimulating immune cells to release pro-inflammatory cytokines such as tumor necrosis factor-α (TNF-α) and interleukin-6 (IL-6) while activating NF- B signaling pathways [**?**]. Reduced synthesis of key neurotrophic factors like nerve growth factor (NGF) and insulin-like growth factor-1 (IGF-1) leads to neuronal apoptosis, affecting axonal regeneration and myelin repair. Additionally, mitochondrial dysfunction results in inadequate ATP production, calcium homeostasis imbalance, and excessive reactive oxygen species generation, further aggravating nerve

cell apoptosis. These pathological changes collectively cause irreversible structural damage to autonomic nerve fibers, including axonal degeneration, demyelination, and ganglion cell apoptosis, ultimately leading to autonomic dysfunction across multiple systems including cardiovascular, gastrointestinal, and urogenital systems (Figure 2 [Figure 2: see original paper]).

Pathogenesis and Clinical Manifestations in Various Organs

The ANS is a tripartite regulatory system composed of sympathetic, parasympathetic, and enteric nerves, extensively distributed in effector organs such as cardiac muscle, smooth muscle, and glands, where it maintains core homeostatic functions. Through finely tuned antagonistic-synergistic mechanisms, the "fight-or-flight" sympathetic and "rest-digest" parasympathetic divisions dynamically balance physiological functions, controlling blood pressure, heart rate, digestion, urination, and thermoregulation.

Cardiovascular System

Diabetic cardiovascular autonomic neuropathy (DCAN) refers to damage of sympathetic and parasympathetic nerves innervating the heart and blood vessels. A characteristic feature of its pathogenesis is sympathetic-parasympathetic imbalance: the vagus nerve (parasympathetic) is affected earliest, with relative sympathetic dominance leading to resting tachycardia in early stages [**?**]. As the disease progresses, sympathetic nerves also become involved, resulting in decreased heart rate variability and late-stage manifestations such as fixed heart rate and orthostatic hypotension. Autonomic imbalance reduces vagal inhibition and causes sympathetic overactivation, elevating catecholamine levels and overactivating the renin-angiotensin-aldosterone system (RAAS) [**?**]. Sympathetic hyperactivity not only exacerbates insulin resistance in a vicious cycle but also exerts detrimental effects on the myocardium, including increased oxygen consumption, ventricular remodeling, and heightened arrhythmia risk [**?**]. Furthermore, hyperglycemia-induced metabolic disturbances play a critical role in DCAN: persistent hyperglycemia and dyslipidemia trigger oxidative stress and systemic inflammation that directly damage autonomic neurons and their blood supply. These mechanisms explain why CAN patients are prone to silent myocardial infarction and sudden cardiac arrest, with significantly elevated 5-year mortality [**?**].

Digestive System

Autonomic neuropathy affecting the digestive tract is termed diabetic gastrointestinal autonomic neuropathy (DGAN), which can cause esophageal dysmotility, gastroparesis, and intestinal motility disorders. Diabetic gastroparesis (DGP), the classic manifestation, primarily results from delayed gastric emptying due to vagal neuropathy and enteric plexus dysfunction [**?**]. Under physiological conditions, the vagus nerve provides crucial regulation:

the proximal stomach maintains continuous vagal tone for food storage, while grinding and peristalsis in the distal stomach are coordinated by autonomically controlled pacemaker cells (interstitial cells of Cajal) [**?**]. In diabetes, vagal nerve injury leads to decompensated gastric motor function, characterized by poor proximal compliance and weak distal propulsion, causing gastric content retention [**?**]. Patients typically experience postprandial upper abdominal fullness, nausea, and vomiting, which subsequently affect glycemic control (as gastroparesis can cause blood glucose fluctuations) [**?**]. Notably, acute hyperglycemia can directly inhibit gastric emptying, while hypoglycemia produces counter-regulatory effects. This physiological feedback is amplified in chronic hyperglycemia, exacerbating gastroparesis symptoms [**?**]. Additionally, studies have shown alterations in local glial support cells and neurotransmitters in the diabetic gastrointestinal tract, such as reduced density of gastric pacemaker cells, degenerative changes in intestinal neurons, and disordered gastrointestinal hormone secretion, suggesting that inflammatory responses and neurotransmitter imbalance also participate in DGP pathogenesis [**?**]. These mechanisms collectively cause gastrointestinal dysmotility in diabetic patients: beyond gastroparesis, vagal nerve injury can cause intestinal motility disorders, with some patients exhibiting alternating constipation-diarrhea syndrome that severely impacts quality of life.

Urogenital System

Autonomic neuropathy affecting the urinary and reproductive systems primarily manifests as bladder dysfunction [**?**]. Diabetic bladder dysfunction (also called diabetic bladder neuropathy or diabetic bladder paresis) is characterized by sacral parasympathetic nerve injury [**?**]. The mechanism involves hyperglycemia-induced degeneration of bladder sensory and motor nerve fibers [**?**], leading to diminished bladder filling sensation, detrusor underactivity, and blunted micturition reflexes. Clinically, early manifestations include urinary frequency, urgency, and even stress or urge incontinence, indicating detrusor overactivity. As nerve damage progresses, bladder sensation becomes impaired, manifesting as increased residual urine and incomplete emptying —signs of low-contractility bladder [**?**]. Typical urodynamic changes include elevated bladder sensation thresholds (larger bladder volume at first urge), decreased detrusor contraction pressure, and increased post-void residual volume. Pathophysiologically, hyperglycemia-induced oxidative stress damages bladder smooth muscle cells and induces apoptosis, accelerating bladder denervation [**?**]. Additionally, chronic polyuria causes bladder overdistension and wall remodeling with thickening, further weakening detrusor contractile function.

Erectile dysfunction (DIED) occurs at high rates in diabetic men and is associated with autonomic nerve damage, primarily manifesting as impaired neural transmission to cavernous tissue. Mechanisms include damage to parasympathetic nerves innervating the corpus cavernosum, reducing vasodilatory signals

required for erection, and sympathetic neuropathy-induced retrograde ejaculation. Female patients may experience decreased libido and vaginal lubrication dysfunction [**?**]. Large prospective studies have confirmed that the presence of cardiac autonomic neuropathy is closely related to sexual dysfunction in both sexes [**?**]. Overall, urogenital autonomic neuropathy often has an insidious onset but profoundly impacts patients' quality of life, requiring heightened clinical attention.

Skin and Peripheral Nerves

DAN can involve the cutaneous microvasculature and glandular regulation. Sympathetic fibers innervating sweat glands and skin vessels are small fibers, and their damage can cause abnormal sweating and blood flow regulation. Typical manifestations include reduced sweating with dry, cracked skin in distal extremities (such as the feet) and compensatory hyperhidrosis in the upper trunk [**?**]. This sudomotor dysfunction (anhidrosis due to autonomic neuropathy) is considered one of the earliest manifestations of diabetic small-fiber neuropathy [**?**]. This pathological change, synergistic with sensory nerve damage, impairs foot skin barrier function. Combined with abnormal microvascular vasomotor reflexes, it exacerbates wound healing impairment and significantly increases the risk of diabetic foot ulcers [**?**]. Additionally, patients with severe peripheral neuropathy may develop Charcot arthropathy, where simultaneous sensory and autonomic nerve damage causes loss of protective joint sensation and blood supply regulation, leading to progressive joint destruction and deformity. Thus, autonomic regulation of skin and distal extremity tissue nutrition is crucial, and its dysfunction is an important factor in diabetic foot syndrome.

In summary, DAN presents a multi-system, heterogeneous clinical spectrum with diverse manifestations across affected organs (Table 1). Although autonomic dysfunction triggered by persistent hyperglycemia shares common initiating factors, susceptibility to damage varies significantly between patients and even between organs in the same patient. Beyond classical metabolic pathways, the gut microbiome microenvironment, local cardiac inflammatory status, and bladder stretch-sensing mechanisms may play key regulatory roles in disease progression. Current clinical diagnosis relies primarily on detecting functional disturbances after they become apparent, often missing the optimal intervention window. Therefore, we need to explore early identification strategies targeting specific autonomic subpopulations or organ-specific biomarkers to shift from symptomatic management to preventive protection.

Treatment Strategies

Glycemic Control and Basic Management

Stringent glycemic control is the fundamental measure for preventing and delaying DN. Studies demonstrate that maintaining near-physiological glucose levels

can effectively reduce DN incidence [**?**]. In type 1 diabetes, intensive insulin therapy significantly lowers the incidence of cardiovascular autonomic neuropathy compared with conventional control (14-year follow-up data show 28.9% CAN incidence in the intensive group versus 35.2% in the conventional group) [**?**]. In type 2 diabetes, intensive glycemic control alone has less pronounced effects on autonomic neuropathy than in type 1 diabetes [**?**], but comprehensive intervention managing multiple risk factors—including blood glucose, blood pressure, and lipids—has demonstrated clear neuroprotective effects. Therefore, early, individualized optimization of glycemic control and management of comorbidities such as hypertension and dyslipidemia constitute the core strategy for preventing autonomic neuropathy.

Pharmacotherapy for Autonomic Function Improvement

Multiple drugs targeting the pathogenesis of autonomic neuropathy have been investigated. Aldose reductase inhibitors (ARIs) reduce hyperglycemia-induced neurotoxic accumulation by blocking the polyol pathway [**?**]. Epalrestat, a widely used ARI in Asia, has been shown in clinical studies to improve symptoms and delay disease progression in DN patients with long-term use [**?**]. Antioxidants such as α-lipoic acid (ALA) exert effects by scavenging free radicals and inhibiting oxidative stress, with multiple trials demonstrating reduced neuropathic pain. Combination therapy with ALA, epalrestat, or mecobalamin shows superior efficacy compared with monotherapy [**?**]. Additionally, microcirculation-improving and neurotrophic agents such as B vitamins (mecobalamin) promote damaged nerve regeneration and repair. Notably, certain diabetes medications may provide additional benefits: RAAS blockers in type 2 diabetes may reduce peripheral neuropathy, presumably through improved vascular function and reduced inflammation [**?**]; novel agents such as sodium-glucose cotransporter 2 (SGLT2) inhibitors and glucagon-like peptide-1 (GLP-1) receptor agonists not only lower glucose but may also benefit autonomic function by reducing oxidative stress and improving cardiovascular status [**?**].

Despite these options, current pharmacotherapy faces the dilemma of "managing symptoms without addressing the root cause." Drugs like epalrestat and ALA can intervene in specific pathways but have limited capacity to reverse established structural nerve damage. Overall, pharmacological treatment should be selected comprehensively based on patient conditions, addressing both hyperglycemia and symptoms such as pain, gastrointestinal dysmotility, and orthostatic hypotension. Current strategies focus primarily on symptom relief, and no specific drug can fundamentally reverse nerve damage. Developing novel agents capable of reversing diabetic nerve injury represents an important future challenge.

Neuromodulation Techniques

With deeper understanding of neural regulation mechanisms, neuromodulation therapies have been applied in DN intervention research. These techniques,

through physical stimulation of autonomic or central neural pathways, hold promise for improving autonomic balance. Notable among these is vagus nerve stimulation (VNS), including invasive cervical VNS and non-invasive transcutaneous auricular VNS. The vagus nerve is the main parasympathetic trunk; stimulating it can initiate anti-inflammatory reflexes, reduce inflammatory cytokine levels [**?**], and influence physiological processes such as insulin secretion and appetite. Animal studies have demonstrated that transcutaneous VNS improves insulin sensitivity and alleviates diabetes-associated depressive-like behaviors [**?**], involving incretin (e.g., GLP-1) release and enhanced pancreatic β-cell function to improve glucose homeostasis [**?**]. Although human studies in diabetic patients remain in early stages, preliminary trials suggest VNS may increase cardiac vagal tone and improve inflammatory status [**?**]. Overall, neuromodulation offers new approaches for refractory DAN, particularly in improving gastrointestinal motility and restoring autonomic balance. However, these technologies remain investigational, requiring more clinical trials to confirm long-term safety and efficacy.

Individualized Treatment

DAN exhibits considerable heterogeneity between patients and involves multiple systems, necessitating individualized treatment plans. Clinical management should develop targeted strategies based on the primary organ systems affected by autonomic involvement: for patients with predominant cardiovascular autonomic neuropathy, beyond glycemic control, close monitoring of heart rate and blood pressure changes is essential to prevent malignant arrhythmias [**?**]. Orthostatic hypotension can be managed with compression measures such as elastic stockings and pressor agents like midodrine. Patients with prominent gastrointestinal autonomic neuropathy require dietary modifications (small, frequent meals; low-fat, low-fiber diet), prokinetic agents (e.g., dopamine antagonists, cisapride) to improve gastric emptying, and avoidance of GLP-1 receptor agonists that may worsen gastroparesis [**?**]. For alternating constipation-diarrhea symptoms, dynamic assessment of the dominant symptom is key, with staged, individualized management strategies using laxatives and antidiarrheals judiciously to break the symptomatic cycle—the goal being improved quality of life rather than completely normal bowel function. Patients with bladder autonomic neuropathy should establish timed voiding habits; for advanced complications such as urinary retention, cholinergic drugs or intermittent catheterization may be combined, with clean intermittent catheterization (CIC) considered the gold standard first-line management. Refractory cases may consider intradetrusor injection of botulinum toxin type A or suprapubic cystostomy. For erectile dysfunction, phosphodiesterase-5 inhibitors may be used with psychological intervention.

Beyond organ-directed symptomatic treatment, individualized care also involves dynamic assessment and follow-up of autonomic functional status. Clinicians can monitor changes in autonomic activity using heart rate variability (HRV)

and other indicators to evaluate efficacy and adjust treatment plans. HRV biofeedback training and regular exercise can enhance autonomic regulation [**?**]. In summary, individualized treatment emphasizes a "patient-centered" approach, selecting the most appropriate multidisciplinary intervention combination based on the extent and severity of autonomic nerve damage to achieve maximal symptom improvement and complication prevention.

Conclusions and Outlook

As a complex phenotype of diabetic nerve injury, DAN often causes multi-system dysfunction involving cardiovascular, digestive, urogenital, reproductive, and cutaneous systems, significantly affecting patient prognosis. Current intervention strategies can prevent or delay autonomic neuropathy development to some extent through strict glycemic control and management of other metabolic risk factors, but lack effective means to reverse established structural nerve damage. This reflects a clear clinical therapeutic bottleneck, with many fundamental questions remaining unanswered.

Although existing research has made progress in multiple metabolic pathways, oxidative stress, and inflammatory responses, the systems biology mechanisms of DAN remain incompletely elucidated. Current research limitations include: (1) most mechanistic studies remain fragmented, lacking integrated understanding of hyperglycemia-induced pathological damage; (2) differential susceptibility of autonomic subpopulations to injury and their underlying molecular mechanisms remain unclear; and (3) few biomarkers are available for early diagnosis and treatment evaluation, with current clinical diagnosis relying primarily on functional tests that identify disease only after significant functional abnormalities appear. These limitations constrain the development of targeted therapeutic strategies.

Therefore, clinical practice should increase emphasis on autonomic neuropathy as a key component requiring active prevention and treatment in diabetes management. Looking forward, research and clinical efforts are addressing several critical questions: how hyperglycemia damages specific autonomic subpopulations through complex metabolic and immune pathways; the specific roles of mitochondrial dysfunction and genetic susceptibility in DAN pathogenesis; and exploration of novel neuromodulation strategies to improve autonomic dysfunction. Clinical practice should emphasize personalized and precision medicine, tailoring prevention and treatment plans based on individual autonomic function assessments. Emerging diagnostic technologies should enable early detection of autonomic damage for timely intervention before irreversible injury occurs.

In conclusion, as understanding of ANS involvement in diabetic complications deepens, we anticipate more comprehensive and effective interventions. Through close integration of basic research and clinical practice, developing innovative therapies based on autonomic nerve modulation and integrating them with traditional metabolic control approaches—while optimizing individualized

protocols for different patients—will ultimately improve prognosis and quality of life for DN patients.

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ORCID: PAN Ziyun https://orcid.org/0009-0006-2132-1112

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