IJCRT.ORG ISSN : 2320-2882

INTERNATIONAL JOURNAL OF CREATIVE RESEARCH THOUGHTS (IJCRT)

An International Open Access, Peer-reviewed, Refereed Journal

DIABETIC NEUROPATHY-A REVIEW

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ABSTRACT

Diabetic neuropathy is a common and early complication of diabetes, but its understanding and effective treatment have presented challenges. The pathophysiology of neuropathy in diabetes is complex, and this, along with the lack of a straightforward treatment regimen, may have contributed to insufficient attention to this complication. However, there have been gradual advancements in the clinical management of diabetic neuropathy, including the proposal of diagnostic criteria and clinical staging for early detection of nerve deficits and treatment guidance.

progress in the pathogenesis of diabetic neuropathy has been made, shedding light on the underlying pathology of this condition. The emergence of pain-relieving agents has also contributed to improving the quality of life for patients experiencing symptomatic neuropathy. Despite these advances, there is still a need for a clearer understanding of the mechanisms leading to the development of diabetic neuropathy, the identification of reliable clinical indices for nerve deficits, and the prediction of prognosis.

In summary, while diabetic neuropathy poses challenges, ongoing research and advancements in clinical management are gradually improving our understanding and ability to address this complication associated with diabetes.

Key Words: Diabetic neuropathy, signs and symptoms, risk factors, treatment

INTRODUCTION

The importance of neuropathy in the clinical management of diabetes is well recognized, but there is a gap in ensuring satisfactory clinical care for this common complication. Several factors contribute to this insufficiency, including the complexity of understanding the clinical status of neuropathy, the absence of highly effective treatment regimens, and a lack of established criteria for evaluating treatment effects.

In this review, the authors aim to address these challenges by discussing the current understanding of the basic pathology and pathogenetic mechanisms underlying diabetic neuropathy. The goal is to establish correlations between the pathologic basis of neuropathy and the clinical signs and symptoms experienced by individuals with diabetes. This approach could potentially lead to a more comprehensive and effective management strategy for diabetic neuropathy by bridging the gap between pathophysiological mechanisms and clinical manifestations.

BASIC PATHOLOGY OF DIABETIC POLYNEUROPATHY

Nerve fiber degeneration and fiber loss:

The most significant alterations in diabetic nerve pathology involve the loss of nerve fibers, particularly with a distal emphasis. Here are key points regarding these changes[1]:

1. Loss of Nerve Fibers: The most prominent and dramatic changes in diabetic nerve pathology include the loss of nerve fibers. This loss exhibits a distal (farther from the center of the body) predominance. This can be observed in the feet and lower extremities.

2. Axonal Degeneration: The degeneration of axons, the elongated parts of nerve cells that transmit signals, is a characteristic feature. This degeneration tends to start in the most distal parts of the axon processes and progresses with the advancement of the disease.

3. Schwann Cell Changes: Schwann cells, which play a crucial role in supporting and insulating nerve fibers, undergo characteristic changes. Dysfunction of Schwann cells contributes to the overall degeneration of nerve fibers.

4. Demyelination: In some cases, there is loss or damage to the myelin sheath that surrounds nerve fibers. Demyelination may occur in areas where there is local pressure or local ischemia/reperfusion injury.

5. Distribution of Degeneration: Distal axonal degeneration initiates in the farthest parts of the nerve fibers and ascends as the disease progresses. All three types of degenerative fibers—axon, Schwann cell, and demyelination—may be encountered in diabetes, but those with distal axonal degeneration are particularly prevalent.

6. Reduction of Small Nerve Fibers: Even in the early stages of diabetes, including the prediabetic stage, there is a reduction of small nerve fibers in the distal foot. The loss of intraepidermal nerve fibers in the skin of the feet parallels the progression of neuropathy.

7. Diagnostic Standard: The evaluation of intraepidermal nerve fibers by skin biopsy has become a worldwide standard for indicating the presence of neuropathy.

These pathological changes reflect the impact of diabetes on the nervous system, particularly in the peripheral nerves, and contribute to the clinical manifestations of diabetic neuropathy.

Skin biopsy, although considered invasive, has been a valuable method for evaluating small fiber neuropathy in diabetic patients[2]. As an alternative, corneal confocal microscopy (CCM) provides a noninvasive means to observe small fibers on the cornea. This diagnostic tool allows for the detection of small fiber regeneration earlier in the cornea than in the skin, as demonstrated in patients with diabetes who underwent pancreas transplantation.

Distal axonal degeneration, a characteristic feature of diabetic neuropathy, is also observed in metabolic neuropathies associated with factors such as vitamin deficiencies and alcoholism. In the context of diabetes, several contributing factors, including metabolic abnormalities and altered blood flow with hypoxia/ischemia or reperfusion, disrupt the integrity of peripheral axons and Schwann cells. This disruption induces degeneration, particularly starting in the most distal part of the nerve fibers. Axons with small diameter are more susceptible to these effects due to their limited supporting system, resulting in the preferential involvement of small-sized nerve fibers. Consequently, symptoms transmitted by these small fibers begin with pain and changes in thermal sensations, followed by paresthesia and sensory loss[3].

ROLE OF MICROANGIOPATHY

The peripheral nerve has a sparse vascular supply compared to other tissues, and its blood flow is primarily regulated by the arteriole at the nerve entry, controlled by sympathetic or peptidergic nerve endings. As a result, the endoneurial area of the nerve is highly vulnerable to ischemia and hypoxia. Research has consistently demonstrated that ischemia and hypoxia play a significant role in the development of neuropathy[6].

Microscopic examination of endoneurial microvessels in diabetic neuropathy often reveals pathological changes, including swollen endothelial cells, narrowing of the lumen, and thickening or duplication of basement membranes in the vascular walls. These vascular alterations are closely associated with the severity of neuropathy, suggesting that microangiopathy contributes to the progression of neuropathy in diabetes. There is a strong correlation between basement membrane thickening and the loss of nerve fibers, emphasizing the role of vascular changes in the development and severity of diabetic neuropathy[7].

RELATIONSHIP BETWEEN NEUROPATHOLOGICAL CHANGES AND CLINICAL SYNDROM

Although there is considerable variability in the clinical signs and symptoms of diabetic neuropathy, recent studies have made progress in elucidating the relationship between these clinical features and underlying pathological changes. Understanding this relationship is crucial for improving the diagnosis and management of diabetic neuropathy.

SUBJECTIVE SYMPTOMS

In diabetic neuropathy, pain is a prominent symptom and can be categorized into inflammatory pain and neuropathic pain. Neuropathic pain is associated with nerve degeneration and fiber loss, typically occurring in the progressive stage of neuropathy. Small nerve fibers, responsible for transmitting pain signals, are often lost in the distal extremities, contributing to a type of phantom pain. Degenerated nerve fibers attempting to regenerate can send pain signals to the spinal cord and, subsequently, to the brain. Various factors, including acute vascular occlusion, rapid changes in blood glucose, or acute energy imbalance, can contribute to pain induction[8].

The type of pain experienced may vary, with dull pain often transmitted by thin fibers (C fibers) and sharp pain by relatively thick fibers (Aδ). Recent research has shown an increased pain threshold in the skin, which is related to decreased density of intraepidermal small nerve fibers. However, the relationship between the density of skin small nerve fibers and the occurrence of spontaneous pain is still under investigation.

As the disease progresses and nerve fiber loss becomes more prominent, a cardinal sign is the loss of sensation, posing a significant risk for foot gangrene or ulcers. Since patients may not always complain about this sign, it is crucial to educate them about the importance of foot care.

OBJECTIVE SIGN AND SYMPTOM ANKLE JERK AND VIBRATION PERCEPTION

For the diagnosis of neuropathy, specific tests such as the ankle jerk and vibration perception test can be useful[9]:

1. Ankle Jerk Test:
   - Loss of ankle jerk is indicative of neuropathy.
   - The absence of ankle jerk reflex is related to the involvement of small unmyelinated afferent nerve fibers that surround muscle spindles.
   - In animals with diabetes, disruption of spiral afferent nerve fibers of the muscle spindle has been observed, potentially leading to an abnormal ankle jerk.
2. Vibration Perception Test (Pressure Test):
   - Vibration perception tests are sensed by Meissner and Pacini corpuscles distributed in the dermis.
   - Meissner and Pacini corpuscles send afferent nerve fibers of Aβ size to spinal dorsal root ganglion cells, and central axons extend to the brain through the dorsal fascicle of the spinal cord.
   - Aging is associated with a decrease in large nerve fiber function, and the number of Pacini corpuscles decreases with age.
   - This reduction in Pacini corpuscles contributes to an increased threshold of vibration perception.

These tests help assess sensory and reflex functions, providing valuable information for the diagnosis and evaluation of neuropathy in individuals, particularly those with diabetes.

AUTONOMIC NERVE SYMPTOM

Understanding the connection between autonomic signs and symptoms and pathological alterations in diabetic neuropathy is challenging. Here are some key points[11]:

1. Pathologic Studies on Autonomic Nervous System:

- Limited pathologic studies on the autonomic nervous system in human diabetes exist.
- Distal axonal degeneration of postganglionic nerve fibers has been reported in these studies.
- This degeneration correlates with abnormal function in various systems such as the gastrointestinal tract, cardiovascular system, and urogenital tracts.

2. Correlation with Autonomic Dysfunction:

- Loss of afferent sensory nerve fibers is associated with specific autonomic dysfunctions, including painless myocardial ischemia, gastroparesis, or atonic bladder.

3. Distinct Changes in Sympathetic Nerves:

- Sympathetic nerves undergo axonal and dendritic dystrophy in diabetic neuropathy.
- Dystrophy is characterized by swollen axons or dendrites containing aggregates of cytoplasmic organelles, mitochondria, endoplasmic reticula, and ribosomes in the axon terminals or dendrites.
- Dystrophic changes are common in diabetes, and their frequency is correlated with the loss of synapses.

4. Prevalence of Dystrophy:

- Dystrophic changes are frequent in diabetes but are also found in normal aging, albeit less frequently.
- The frequency of dystrophy is well correlated with the loss of synapses.

These findings highlight the complex relationship between autonomic neuropathy and pathological alterations in diabetic individuals, emphasizing the need for further research to enhance our understanding of these connections.

RISK FACTORS IN DIABETIC NEUROPATHY

The importance of blood glucose control in the onset and progression of neuropathy in patients with type 1 diabetes is well-established, as indicated by the Diabetes Control and Complications Trial (DCCT) studies and subsequent Epidemiology of Diabetes Interventions and Complications (EDIC) studies. In addition, a European epidemiologic prospective study on neuropathy in type 1 diabetes over five consecutive years revealed several risk factors for the progression of neuropathy:

1. Long-Term Blood Glucose Control (HbA1c):

- Maintaining optimal blood glucose levels, as indicated by glycated hemoglobin (HbA1c), is crucial for preventing and slowing the progression of neuropathy.

2. Hypertension:

- High blood pressure is identified as a risk factor for the progression of neuropathy. Managing hypertension is important in comprehensive diabetes care.

3. Lipidemia:

- Abnormal lipid levels contribute to the risk of neuropathy progression. Controlling lipid levels is recommended to mitigate this risk.

4. Smoking:

- Tobacco smoking is recognized as a risk factor for the progression of neuropathy. Smoking cessation is encouraged for individuals with diabetes.

5. Obesity:

- Obesity is identified as a risk factor for the progression of neuropathy. Maintaining a healthy weight through lifestyle interventions is beneficial.

These findings underscore the multifactorial nature of neuropathy progression in type 1 diabetes and emphasize the importance of addressing various risk factors, including blood glucose control, hypertension, lipid levels, smoking, and obesity, to effectively manage and prevent diabetic neuropathy[13].

BIOMECHANICAL CHANGES FOR PERIPHERAL NERVE DAMAGE IN DIABETES

The mechanisms through which hyperglycemia leads to peripheral nerve damage in diabetic neuropathy are complex and multifaceted. Chronic hyperglycemia triggers various metabolic pathways that contribute to the development of neuropathy. Several key metabolic pathways activated in response to prolonged elevated glucose levels play a role in peripheral nerve damage. Here are some of these pathways:

1. Polyol Pathway:

The polyol pathway, also known as the aldose reductase pathway, is a metabolic pathway that plays a role in the metabolism of glucose. It involves the conversion of glucose to sorbitol and, subsequently, to fructose. The key enzyme in this pathway is aldose reductase.Here's an overview of the polyol pathway:

1. Glucose to Sorbitol (Catalyzed by Aldose Reductase): Aldose reductase catalyzes the reduction of glucose to sorbitol using NADPH as a cofactor. This reaction consumes NADPH in the process. Reaction:Glucose + NADPH + H^+ → Sorbitol + $NADP^+$

2. Sorbitol to Fructose (Catalyzed by Sorbitol Dehydrogenase): Sorbitol dehydrogenase catalyzes the oxidation of sorbitol to fructose. This reaction also involves the conversion of NAD^+ to NADH. Reaction: Sorbitol + NAD^+ → Fructose + NADH + H^+ The polyol pathway occurs in various tissues, and its activation is particularly relevant in conditions of hyperglycemia, such as diabetes. The significance of this pathway lies in its potential contribution to diabetic complications, including neuropathy.

Implications in Diabetes:

In diabetes, where blood glucose levels are elevated, the polyol pathway becomes more active. The increased flux through this pathway has several implications:

- Accumulation of Sorbitol: Sorbitol, being impermeable to cell membranes, can accumulate within cells. This accumulation is especially notable in tissues with limited sorbitol dehydrogenase activity.

- Consumption of NADPH: The reduction of glucose to sorbitol consumes NADPH. NADPH is an important cofactor in various cellular processes, including antioxidant defense mechanisms.

- Formation of Fructose: The conversion of sorbitol to fructose also has implications for the formation of advanced glycation end products (AGEs), which are associated with diabetic complications.

- Osmotic Stress: The accumulation of sorbitol can lead to osmotic stress within cells, affecting cell function and contributing to complications.

The polyol pathway is just one of several pathways implicated in the pathogenesis of diabetic complications. Understanding these pathways is crucial for developing targeted therapeutic approaches to mitigate the impact of diabetes on various tissues and organs.

2. NON ENZYMATIC GLYCATION(AGE/RAGE):

The process you're describing involves the formation of advanced glycation endproducts (AGEs) in the context of diabetes, which has implications for various tissues, including peripheral nerve tissues. Here's an overview:

1. Formation of Intermediate Glycated Proteins (Amadori Products): When there is excess glucose in the body, it can bind to the amino groups of proteins, forming Amadori products. These are intermediate glycated proteins.

2. Advanced Glycation Endproducts (AGEs):Amadori products can undergo further reactions, leading to the formation of advanced glycation endproducts (AGEs). These are large, insoluble molecules that result from the cross-linking of glycated proteins.

3. Toxicity of Intermediate Glycation Products: Intermediate glycation products, such as methylglyoxal (MG) and 3-deoxyglucosone (3-DG), are shown to be toxic to neural tissues. They can produce reactive oxygen species (oxygen radicals), contributing to cell death or dysfunction.

4. Pain Induction in Diabetic Neuropathy:MG, one of the intermediate glycation metabolites, is implicated in mediating pain induction in diabetic neuropathy.

5. Concurrent Vitamin Deficiency and Metabolic Imbalance: The process of AGE formation is associated with concurrent vitamin deficiency and metabolic imbalance.

6. Accumulation of AGEs: AGEs accumulate in various components of peripheral nerve tissues. Long-lived proteins, especially basement membrane proteins, are susceptible to AGE accumulation.

7. Impact on Nerve Fiber Degeneration and Regeneration: The accumulation of AGEs can lead to nerve fiber degeneration and impair nerve fiber regeneration. This has implications for the structural integrity and function of peripheral nerves.

8. AGE-Receptor Interactions (RAGE): AGEs can bind to their receptors, known as RAGE (receptor for AGE). RAGE is expressed in various cells within the peripheral nerve, including neuronal cells, Schwann cells, and endothelial cells.

9. Activation of NADPH Oxidase and NF-κB: Following the binding of AGEs to RAGE, there is activation of NADPH oxidase, leading to the release of reactive oxygen species. This activation, in turn, triggers the activation of NF-κB, resulting in proinflammatory reactions.

The interplay of these processes contributes to the development and progression of diabetic neuropathy. Understanding these mechanisms is crucial for developing targeted therapeutic strategies to mitigate the impact of diabetes on neural tissues.

- Elevated glucose levels contribute to the formation of advanced glycation end products. These molecules result from non-enzymatic reactions between glucose and proteins, leading to the cross-linking and modification of proteins. AGEs can impair cellular function and contribute to oxidative stress.

3. PROTEIN KINASE C PATHWAY

Protein kinase C (PKC) is a family of enzymes that plays a crucial role in various cellular functions, including protein synthesis and calcium metabolism. There are different isoforms of PKC, and they are denoted by Greek letters such as α, β, δ, γ, etc.

In the context of hyperglycemia and diabetes, the expression of specific PKC isoforms can be altered, contributing to the development of complications in various tissues. Here's a summary of the role of PKC in diabetic complications:

1. PKCβ and Vascular Tissues:

- In hyperglycemic conditions, there is an increase in the expression of PKCβ in vascular tissues, such as the eyes and renal tissues.

- Increased PKCβ activity is associated with vascular complications, including increased vascular permeability, perturbed vascular supply, and ischemia.

- PKCβ has been implicated in the development of diabetic retinopathy and nephropathy.

2. Experimental Trials and PKCβ Inhibitors:

- Experimental trials using PKCβ inhibitors have shown success in improving pathological alterations in the eyes and kidneys of diabetic animals.

- These inhibitors have demonstrated positive effects on diabetic retinopathy and nephropathy in preclinical studies.

3. Neuropathy and PKCβ Inhibition:

- In diabetic neuropathy, there was improvement in nerve conduction velocity (NCV) and nerve blood flow in diabetic rats treated with a PKCβ inhibitor.

- This suggests a potential role for PKCβ in the development of diabetic neuropathy.

4. Phase III Clinical Trial Outcome:

- Despite promising results in preclinical studies, a phase III clinical trial of a PKCβ inhibitor was unsuccessful.

- Clinical trials may face challenges and complexities that were not observed in preclinical settings.

5. Tissue-Specific Changes in PKC Isoforms:

- There is a difference in the response of PKC isoforms between neural and vascular tissues.

- While vascular tissues show increased expression of PKCβ and increased PKC activity, neural tissues exhibit decreased expression of PKCα and lowered PKC activity.

6. Importance of Tissue-Specific Targeting:

- Targeting specific PKC isoforms in different tissues may be essential to achieve better efficacy.
- Tissue-specific inhibitors may be required to address the distinct changes in PKC isoforms observed in neural and vascular tissues.

Understanding the complex role of PKC in diabetes-related complications and developing targeted therapeutic strategies remains an area of active research and clinical investigation[26].

6. HEXOSAMINE PATHWAY:

The hexosamine pathway is a metabolic pathway that has gained increasing interest as a potential causative mechanism for the development of diabetic complications. Here's an overview of the hexosamine pathway and its potential role in diabetic complications, including neuropathy:

1. Hexosamine Pathway Activation:
   - Excessive glucose entering the cell is converted to glucose-6-phosphate.
   - Glucose-6-phosphate is further converted to fructose-6-phosphate.
   - Fructose-6-phosphate is then converted to glucosamine 6-phosphate (GlcN6-P) by the enzyme glutamine/fructose-6-phosphate-amido-transferase (GFAT).
2. Glycosylation and Cellular Modification:
   - GlcN6-P is involved in the glycosylation of crucial cellular proteins.
   - Glycosylation refers to the attachment of a glycosyl chain to molecules in the nucleus, cytoplasm, and cell membrane.
   - This glycosylation process can lead to altered cell function and cell injury.
3. Hyperglycemia-Induced Activation:
   - Hyperglycemia induces the activation of GFAT and subsequent glycosylation of cellular proteins.
   - The activation of the hexosamine pathway is associated with cellular changes and injury.
4. Inhibition of GFAT and Prevention of Cell Injury:
   - In studies where GFAT was inhibited by a specific inhibitor, glycosylation was suppressed.
   - Inhibition of GFAT prevented cell injury in experimental settings.
5. Effects on Nerve Conduction Velocity (NCV) and Neuronal Cells:
   - Animals given glucosamine, a product of the hexosamine pathway, developed delayed NCV.
   - Cultured neuronal cells exposed to glucosamine underwent apoptosis (programmed cell death).
6. Role in Neuropathy and Unknown Pathway Details:
   - The precise metabolic pathway of the hexosamine pathway is not yet fully understood.
   - The specific role of the hexosamine pathway in the development of diabetic neuropathy is still unknown and requires further investigation.
7. Clinical Implications:
   - The hexosamine pathway may represent a potential target for therapeutic interventions to prevent or mitigate diabetic complications.

- Understanding the pathway's role in neuropathy could provide insights into novel treatment strategies.

Research in this area is ongoing, and unraveling the complexities of the hexosamine pathway and its contribution to diabetic complications, including neuropathy, remains an active area of investigation[28].

5. OXIDATIVE STRESS:

Oxidative stress has been recognized as a significant contributor to the pathogenesis of diabetic complications. While its role in vascular complications and effects on endothelial and smooth muscle cells are well-established, there are still unresolved questions regarding its impact on neurological complications in diabetes.

1. Controversy on the Source of Oxidative Stress:

- There is ongoing debate about the primary source of oxidative stress in diabetic neuropathy.
- Recent studies have indicated decreased energy production (ATP production) in nerve mitochondria and less production of oxygen stress in diabetic nerves.

2. Alpha-Lipoic Acid as an Antioxidant:

- In Germany, alpha-lipoic acid, an antioxidant, has been clinically applied for the treatment of neuropathy based on the premise that oxidative stress plays a major role.
- Short-term studies reported improvements in subjective symptoms.

3.Clinical Trials and Approval Status:

- Despite positive outcomes in short-term studies, double-blind clinical trials have not definitively confirmed the efficacy of alpha-lipoic acid.
- As a result, alpha-lipoic acid has not been universally approved as an effective treatment for diabetic neuropathy.

The controversy surrounding the source of oxidative stress and the complex nature of diabetic neuropathy pose challenges in establishing universally effective treatments. Ongoing research aims to unravel the intricate mechanisms involved in neuropathy and oxidative stress, providing insights into potential therapeutic targets[15].

7 .CYTOKIKNE NEUTROPHILIC FACTOR:

The inflammatory process is enhanced in diabetic tissues, including the peripheral nerves, leading to increased infiltration of macrophages and excessive production of inflammatory cytokines. Among these cytokines, TNF-α, IL-1α, and IL-1β are elevated in diabetic nerves and have cytotoxic effects, contributing to neurodegeneration. Some potential interventions for experimental diabetic neuropathy in animals include TNF-α antagonists or cyclooxygenase (COX)-2 inhibitors, although their efficacy in humans is still under investigation.

Additionally, studies have revealed deficiencies in the production and release of neurotrophic factors, such as nerve growth factor, neurotrophin 3, and ciliary neurotrophic factor (CNTF), in diabetic animals. The administration of erythropoietin derivatives has shown effectiveness in addressing functional and structural deficits in diabetic animals. However, it remains unclear whether the deficit of neurotrophic factors is the primary cause of neuropathy or a consequence of nerve damage in diabetes[29].

The complex interplay between inflammatory processes and neurotrophic factors in diabetic neuropathy necessitates further research to understand the underlying mechanisms and develop targeted therapeutic approaches for both prevention and treatment. Clinical confirmation of the effectiveness of these interventions in humans is crucial for their translation into practical treatments for diabetic neuropathy[30].

DIRECTION OF TREATMENT

The final goal of diabetes treatment is to maintain a good quality of life and healthy life expectancy. Achieving this goal involves preventing the clinical onset of neuropathy and inhibiting the progression of symptomatic neuropathy. To do so, a precise understanding of the pathogenesis of neuropathy is crucial for establishing fundamental treatments.

In managing diabetic neuropathy, a clear distinction should be made between care and cure. For patients who already have established neuropathy, the main focus is on care, which is palliative in nature. Pain control becomes a major concern in providing care, and recent developments in analgesics or antidepressants have improved the quality of pain management. However, further advancements are still needed in this area.

On the other hand, when it comes to preventing the progression or reversing neuropathy, the available means are still in an early stage. Developing effective treatments for cure requires a thorough understanding of the natural history of neuropathy and the establishment of appropriate clinical endpoints. Without this knowledge, candidate compounds based on pathogenetic mechanisms may prove effective in animal models but may not translate well to human treatment.

In summary, addressing the symptoms and providing care, particularly in terms of pain control, is a primary focus for those with established neuropathy. However, efforts to develop treatments that can prevent progression or achieve reversal are still in the early stages and require a deeper understanding of the natural history of neuropathy in diabetic patients.

CONCLUSION

The conclusion emphasizes the importance of understanding the pathogenesis of diabetic neuropathy to develop effective treatments for both symptom management and disease modification. Currently, care, especially pain control, plays a significant role in addressing the symptoms of established neuropathy. However, efforts to prevent progression or achieve reversal are still in the early stages and require further research.

The review suggests that the ultimate goal of diabetes treatment is to maintain a good quality of life and healthy life expectancy. To achieve this goal, it is essential to clarify the natural history of neuropathy and establish appropriate clinical endpoints. The distinction between care and cure is highlighted, emphasizing the need for both palliative measures and efforts to develop treatments that address the underlying causes of neuropathy.

In summary, the conclusion underscores the ongoing challenges in managing diabetic neuropathy and the necessity for continued research to improve the quality of life for individuals with diabetes.

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