# Chapter 3
# Diabetic Neuropathy

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**Abstract** Neuropathy is the most common and earliest to occur among a variety of vascular complications of diabetes. In contrast to its popularity, it seems that attention has not been sufficiently paid to this complication. This may have been ascribed to the difficulty in understanding of the pathophysiology of neuropathy or lack of effective treatment regimen due in part to the complicated etiology. Nevertheless, there are slow but steady advances in clinical management of diabetic neuropathy involving the proposal of diagnostic criteria or clinical staging of neuropathy for an early detection of nerve deficits and direction of the treatment. Emergence of pain-relieving agents has also contributed to the improvement of quality of life in patients with symptomatic neuropathy. Notwithstanding, there still needs clarification of the pathogenesis for the development of diabetic neuropathy, clinical indices for nerve deficits, and for the prediction of prognosis. In this communication, recent progress in the pathogenesis of diabetic neuropathy will be summarized and its underlying pathology will be introduced.

**Keywords** Diabetic neuropathy • Pathology • Pathogenesis

## 3.1 Introduction

Importance of neuropathy is well understood in clinical practice of diabetes management. It is not always the case, however, that clinical care for this common complication is satisfactory. The reason for the insufficiency of clinical attention may be ascribed to the difficulty in the understanding of the clinical status of neuropathy or

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lack of effective treatment regimens for neuropathy. Alternatively, it may also be attributed to the lack of established criteria for the evaluation of the treatment effects. In this review, we will refer to the current consideration on the basic pathology and pathogenetic mechanisms of diabetic neuropathy and attempt to correlate the pathologic basis with clinical signs and symptoms.

## 3.2 Basic Pathology of Diabetic Polyneuropathy

### *3.2.1 Nerve Fiber Degeneration and Fiber Loss*

Most dramatic changes in diabetic nerve in humans are represented by loss of nerve fibers with distal predominance (Table 3.1) [1]. Axonal degeneration and Schwann cell changes are characteristic. Demyelination also appears where there is a local pressure or local ischemia/reperfusion injury. Distal axonal degeneration starts in the most distal portion of the axon processes, and degeneration will ascend with progression of the disease. In diabetes, all three types of degenerative fibers may be encountered. However, most prevalent are fibers with distal axonal degeneration. Reduction of small nerve fibers in the distal foot occurs in early stage of diabetes, even in prediabetic stage [2]. The loss of intraepidermal nerve fibers well parallels with progression of neuropathy [3]. Currently, evaluation of intraepidermal nerve fibers by skin biopsy becomes world standard indicative of presence of neuropathy.

**Table 3.1** Pathologic features of diabetic neuropathy

| | Large fiber lesions | Small fiber lesions | Microvessel changes |
|---|---|---|---|
| Somatic nerves | | | |
| (Sural nerve) | Distal nerve fiber loss<br>(focal and diffuse)<br>Axonal degeneration<br>Demyelination | Loss of small fibers | Luminal occlusion<br>Swollen endothelial cells<br>Thickened basement membrane |
| (Skin) | | Loss and disruption of nerve fibers | Fenestration |
| (Cornea) | | Loss of nerve fibers | |
| | | Loss of branching | |
| Autonomic nerves | | | |
| (Parasympathetic) | | Postganglionic | |
| | | Nerve fiber loss | |
| (Sympathetic) | | Axonal dystrophy | |
| | | Loss of synapses | |
| Clinical phenotype | Ankle jerk↓ | Thermal sensation↓ | |
| | Perception↓ | Pain sensation↓ | |
| | Vibration sense↓ | Spontaneous pain | |
| | Nerve conduction↓ | | |
| | Amplitudes↓ | | |

However, as skin biopsy is claimed to be still invasive, alternative noninvasive observation of small fibers on the cornea (corneal confocal microscopy, CCM) has been established as a diagnostic tool for the small fiber neuropathy. With this method, regeneration of small fibers could be detected earlier in cornea than in the skin in patients with diabetes who undertook pancreas transplantation [4].

Distal axonal degeneration is known to occur in cases of metabolic neuropathies including vitamin deficiencies and alcoholism [1]. In diabetes, in addition to metabolic aberration, altered blood flow with hypoxia/ischemia or reperfusion perturbs the integrity of peripheral axons and Schwann cells and thereby induces the degeneration starting in the most distal part [5]. Axons with small diameter are preferentially affected because of limited supporting system due to its small size. Consequently, symptoms transmitted by small-sized nerve fibers commence with pain and alterations of thermal sensations, followed by paresthesia as well as sensory loss.

### *3.2.2 Role of Microangiopathy*

Vascular supply is sparse in the peripheral nerve compared to other tissues. Neural regulation of blood flow is limited to the arteriole at the entry in the nerve which is controlled by sympathetic or peptidergic nerve endings. Consequently, endoneurial area of the nerve is extremely susceptible to ischemia/hypoxia [6]. It was repeatedly shown that ischemia/hypoxia greatly contributes to the development of neuropathy. In fact, endoneurial microvessels show swollen endothelial cells, narrowing of the lumen, and thickening/duplication of basement membranes of the vascular walls [7]. The vascular changes well correlated with the severity of neuropathy, indicating that microangiopathy promotes the progression of neuropathy in diabetes. In fact, there is a close correlation between basement membrane thickening and nerve fiber loss.

## 3.3 Relationship Between Neuropathological Changes and Clinical Syndrome

Despite of considerable variability for the clinical signs and symptoms, recent studies slowly but steadily shed light on the relationship between clinical features and pathologic changes.

### *3.3.1 Subjective Symptoms*

The most prominent symptom in diabetic neuropathy may be pain as a positive symptom. Pain in diabetic polyneuropathy is roughly divided into inflammatory pain and neuropathic pain. The latter of which is ascribed to nerve degeneration

and nerve fiber loss and occurs in progressive stage of neuropathy. In this setting, small nerve fibers are responsible to convey pain signals, but in the lower extremities, such fibers are largely lost in distal site. Thus, the pain may be accounted for by a reflection of phantom pain [8]. Under such circumstances, degenerated nerve fibers that attempt to regenerate send pain signals to dorsal column of the spinal cord through dorsal root ganglia. Ascending nerve fibers from dorsal column to the central nervous system also carry pain to the brain. A variety of factors are also involved in pain induction such as acute vascular occlusion, rapid changes of blood glucose, or acute energy imbalance. Thin fibers (C fibers) usually transmit dull pain while sharp pain is conveyed by relatively thick fibers (Aδ). Recently, pain threshold of the skin was found to be increased and related to decreased density of intraepidermal small nerve fibers. It is still open to question, however, whether the density of skin small nerve fibers is in fact related to the occurrence of spontaneous pain.

With advancement of the disease, as loss of nerve fibers becomes more prominent, loss of sensation is a cardinal sign which is a strong risk for foot gangrene or ulcer. Since patients do not complain on this sign, every effort should be made to educate the importance of foot care to the patients (Fig. 3.1).

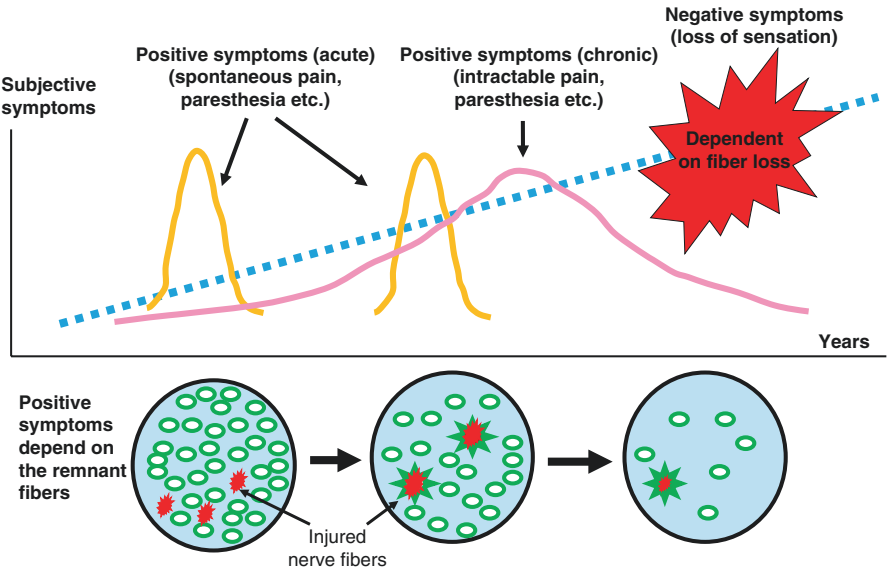


**Fig. 3.1** Natural history of diabetic neuropathy and its relationship to positive and negative symptoms. With background of progressive decline of nerve fibers, patients with diabetes complain pain and paresthesia in the foot which are triggered by injured nerve fibers. Acute pain is induced by rapid metabolic deterioration or vascular impairments that cause rapid processes of nerve fiber degeneration which sends pain signals. Pain also appears chronically as consequence of long-term nerve injury. Such positive symptoms are caused by remnant nerve fibers that convey pain signals. On the other hand, negative symptoms of loss of sensation are caused by loss of nerve fibers and patients usually do not complain. Therefore, this condition is more serious for prognosis

### 3.3.2 *Objective Signs and Symptoms; Ankle Jerk and Vibration Perception*

Ankle jerk and vibration perception test are useful for the diagnosis of neuropathy. Loss of ankle jerk is dependent on the involvement of small unmyelinated afferent nerve fibers that surround muscle spindles. Spiral afferent nerve fibers of the muscle spindle were found to be disrupted in animals with diabetes [9], possibly resulting in abnormal ankle jerk.

Vibration perception test or pressure test are sensed by Meissner and Pacini corpuscles distributed in the dermis. These corpuscles send afferent nerve fibers of Aβ size to spinal dorsal root ganglion cells and then central axons extend to the brain through dorsal fascicle of the spinal cord. It is known that aging is associated with decreased large nerve fiber function. In fact, the number of Pacini corpuscles is decreased with aging [10], resulting in increased threshold of vibration perception.

### 3.3.3 *Autonomic Nerve Symptoms*

Connection of autonomic signs and symptoms with pathologic alterations is challenging in diabetic neuropathy. There are only a few pathologic studies on autonomic nervous systems in human diabetes. In their studies, distal axonal degeneration of postganglionic nerve fibers was reported to correlate with abnormal function of gastrointestinal tract, cardiovascular system, and urogenital tracts. Loss of afferent sensory nerve fibers is relevant to painless myocardial ischemia or gastroparesis or atonic bladder.

Most distinct changes in sympathetic nerves are axonal and dendritic dystrophy which is swollen axon or dendrite containing aggregates of cytoplasmic organelles, mitochondria, endoplasmic reticula, and ribosomes in the axon terminals or dendrites [11]. Dystrophic changes are frequent in diabetes but also found in normal aging although less frequently. The frequency of dystrophy was well correlated with loss of synapses.

## 3.4 Risk Factors for Diabetic Neuropathy

It is well established from Diabetes Control and Complications Trial (DCCT) studies and subsequent Epidemiology of Diabetes Interventions and Complications (EDIC) studies that blood glucose control is critical to the onset and progression of neuropathy in patients with type 1 diabetes. Also in Europe, epidemiologic prospective study on neuropathy in type 1 diabetes for consecutive 5 years demonstrated that long-term blood glucose control (HbA1c), hypertension, lipidemia, smoking, and obesity were found to be risk factors for the progression of neuropathy

**Table 3.2** Risk factors of neuropathy development in patients with type 1 diabetes[a]

| Risk factors | Odd's ratio (CI) | *p* value |
|---|---|---|
| Model 1 | | |
| Duration of diabetes | 1.40 (1.21–1.63) | $p < 0.001$ |
| HbA1c | 1.48 (1.23–1.79) | $p < 0.001$ |
| HbA1c (Δ) | 1.36 (1.14–1.62) | $p = 0.001$ |
| Triglyceride | 1.21 (1.02–1.40) | $p = 0.03$ |
| Total cholesterol | 1.15 (0.98–1.35) | $p = 0.08$ |
| BMI | 1.27 (1.08–1.47) | $p < 0.001$ |
| Smoking history | 1.38 (1.03–1.85) | $p = 0.03$ |
| Hypertension | 1.57 (1.03–2.39) | $p = 0.03$ |
| Albumin excretion rate | 1.01 (0.88–1.14) | $p = 0.93$ |
| Model 2 | | |
| Duration of diabetes | 1.25 (1.03–1.51) | $p = 0.02$ |
| HbA1c | 1.64 (1.33–2.03) | $p < 0.001$ |
| HbA1c(Δ) | 1.44 (1.17–1.77) | $p = 0.001$ |
| Triglyceride | 1.17 (0.97–1.41) | $p = 0.10$ |
| Total cholesterol | 1.11 (0.93–1.54) | $p = 0.25$ |
| BMI | 1.20 (1.01–1.43) | $p = 0.04$ |
| Smoking history | 1.68 (1.20–2.36) | $p = 0.003$ |
| Hypertension | 1.54 (0.96–2.47) | $p = 0.07$ |
| Cardiovascular disease | 2.12 (1.16–3.86) | $p = 0.01$ |
| Retinopathy | 1.45 (0.98–2.13) | $p = 0.06$ |
| Albumin excretion rate | 1.02 (0.89–1.18) | $p = 0.75$ |

Model 1 was the result of 1101 cases with inclusion of albumin excretion rate but without cardiovascular disease, and Model 2 was the result of 932 cases with inclusion of cardiovascular diseases and retinopathy but without albumin excretion rate

[a]Modified from Reference [12]

(Table 3.2) [12]. In contrast to type 1 diabetes, however, it is yet to be established whether long-term hyperglycemia is a critical determinant for the development of neuropathy by UKPDS study. Recent studies disclosed possible implication of hyperlipidemia and hypertension as contributing factors for neuropathy [13].

## 3.5 Biochemical Mechanisms for Peripheral Nerve Damage in Diabetes

It is yet to be clear how hyperglycemia leads to peripheral nerve damage. Basically, increased flux of glucose into collateral glycolytic pathway is a major process which is still complicated. In this review, we will introduce several key metabolic pathways which are known to be activated in chronic hyperglycemia, contributing to the development of neuropathy (Fig. 3.2).

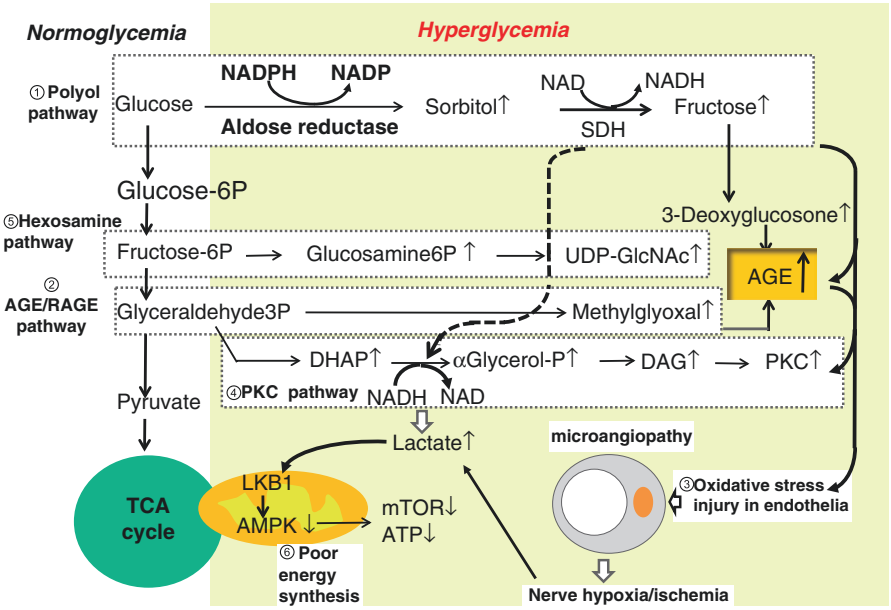


**Fig. 3.2** Proposed mechanisms of how hyperglycemia affects the peripheral nerve. In normoglycemia, intracellular glucose undergoes glycolysis through TCA cycle in mitochondria to produce ATP. Once hyperglycemia occurs, polyol pathway is activated (*1*) to produce sorbitol and fructose. Hyperglycemia also elicits nonenzymatic glycation and AGE formation via intermediate glycation products like 3-deoxyglucosone and methylglyoxal (*2*). AGE binds with receptor for AGE (RAGE) releasing NADPH oxidase and activation of NF-κB. These pathways exert oxidative stress damage to the endothelial cells and nerve tissues (*3*). Hyperglycemia also elicits activation of protein kinase C via production of diacylglycerol (*4*). It was also pointed out that increased fructose-6-P and glutamate-6-P undergo excessive glycosylation of nuclear, membranous proteins leading to O-GlcNAc glycosylation of cellular proteins, thus modifying cellular function (*5*). Recently, excessive lactate production in the nerve was found to associate with reduced AMPkinase (AMPK) with suppression of mTOR and ATP synthesis (*6*)

### *3.5.1 Polyol Pathway (Aldose Reductase Pathway)*

The first collateral pathway of glycolysis in hyperglycemia is polyol pathway. Excessive flux of glucose is converted to sorbitol mediated by aldose reductase (AR) [14]. Sorbitol is impermeable and thereby accumulates in the cell. Then the sorbitol is converted into fructose via sorbitol dehydrogenase (SDH). As the first step of this pathway progresses, there occurs much consumption of nicotinamide adenine dinucleotide phosphate (NADPH) acting as coenzyme of AR. NADPH is also utilized for the production of reduced glutathione (GSH) as a scavenger of oxygen radicals and for the production of nitric oxide (NO) which is derived from L-arginine. Following the consumption of NADPH, as a consequence of deficient GSH and NO, excessive oxygen radicals and insufficient NO with impaired

endoneurial function affect the peripheral nerve tissues, resulting in neuropathic changes. Recent studies also disclosed complicated metabolic interplay between impaired mitochondrial energy production and redox alteration incurred by increased flux of polyol pathway [15]. In this setting, excessive lactate production suppresses AMP-activated protein kinase (AMPK) to inhibit serine-threonine kinase (mTOR, mammalian target of rapamycin) activation, resulting in poor energy production. It is intriguing that mice deficient in liver kinase B1 (LKB1) as an upstream molecule of AMPK develop sensory neuropathy reminiscent of typical diabetic neuropathy in humans [16]. Further investigation is expected to solve the relationship between LKB1-AMPK and diabetic neuropathy.

Clinical application of AR-inhibitors (ARI) showed benefits for improvement of delayed nerve conduction velocity (NCV) and promotion of nerve fiber regeneration. Although ARI developed in Western countries were given up to develop on the market because of potential adverse effects or insufficient efficacy, epalrestat marketed in Japan was found to be effective showing significant suppression of the progressive delay of NCV [17]. The failure of the clinical trial of ARI may be ascribed to the inappropriate inclusion of subjective symptoms as clinical endpoint because symptoms do not necessarily parallel with the progression of the disease.

### *3.5.2 Nonenzymatic Glycation (AGE/RAGE) Pathway*

Superfluous glucose is likely to bind with amino acid base of structural proteins in the body forming Amadori products of intermediate glycated proteins. Glycated proteins further cross-link with each other to aggregate as insoluble large molecules, called advanced glycation endproducts (AGE). There are plenty of suggested mechanisms that account for the implication of protein glycation in the development of neuropathy in diabetes. As early glycation products, intermediate glycation products such as methylglyoxal (MG) and 3-deoxyglucosone (3-DG) are shown to be toxic to neural tissues. These intermediate glycation metabolites produce oxygen radicals to exert cell death or dysfunction. It was also found that MG mediates pain induction in diabetic neuropathy [18]. During the course of AGE formation, there also occur concurrent vitamin deficiency and metabolic imbalance [19]. In addition to intermediate glycation products, AGE accumulate in various components of peripheral nerve tissues to induce cell damage and degeneration of structural proteins. Long-lived proteins such as basement membrane proteins are likely to undergo AGE accumulation, resulting in nerve fiber degeneration and impaired nerve fiber regeneration. Furthermore, bindings of AGE and their receptors (RAGE, receptor for AGE) also elicit cell biological reactions to cause cell damage [20]. RAGE is expressed diffusely in the peripheral nerve, in particular cell membranes of neuronal cells, Schwann cells, and endothelial cells [21]. Following the attachment of AGE with RAGE, NADPH oxidase is activated to release OH radicals (NADPH activation). As a consequence, NF-κB is activated to exert proinflammatory reaction [22].

When RAGE is transgenetically overexpressed in endothelial cells, nerve conduction delay is further worsened in diabetic mice [21], whereas NCV delay and nerve fiber atrophy were mitigated in RAGE-deficient diabetic mice compared to wild diabetic mice, thus implicating in the AGE/RAGE role in the development of neuropathy [23]. Administration of AGE was recently found to induce NCV delay and nerve fiber atrophy in normal rats, similar to those found in diabetic animals, confirming a pathogenic role of AGE in the development of neuropathy [24]. AGE is known to be elevated in the serum of patients with end-stage renal failure who show the delay of NCV.

There have been attempts of inhibition of glycation process and AGE/RAGE action for the prevention and treatment of diabetic complications. Treatment with aminoguanidine demonstrated the inhibition of AGE accumulation in the nerve, improvement of nerve blood flow, and NCV delay as well as nerve fiber lesions [25]. More recently, benfotiamine, a derivative of vitamin B1, and pyridoxamine, a vitamin B6 derivative, are examined for their efficacy on the neuropathy by clinical trials [19]. No definite clinical efficacy was obtained in these trials.

### *3.5.3 Protein Kinase C Pathway*

Protein kinase C (PKC) plays a central role in the protein synthesis and Ca metabolism in nerve cells. There are many isoforms of PKC such as α, β, δ, γ, and so on. In hyperglycemic condition, there is an increase in the expression of PKCβ in the eye and renal tissues of diabetic animals with increased vascular permeability, perturbed vascular supply, and ischemia, thus contributing to the development of retinopathy and nephropathy in diabetes. Experimental trials with PKCβ inhibitor successfully improved pathological alterations in the eye or kidney. Also in neuropathy, there was improvement of NCV and nerve blood flow in STZ-induced diabetic rats treated with PKCβ inhibitor. However, phase III clinical trial of PKCβ inhibitor was unsuccessful.

It is of note that there is a difference in PKC changes between neural and vascular tissues. While vascular tissues were associated with increased expression of PKCβ and increased PKC activity, neural tissues showed decreased expression of PKCα and lowered PKC activity [26]. It is therefore likely that targeting the tissues with specific PKC-isoform inhibitor may be essential to obtain better efficacy.

### *3.5.4 Hexosamine Pathway*

There is an increasing interest in the hexosamine pathway as a causative mechanism for the development of diabetic complications [27]. When excessive glucose enters the cell, it is converted to glucose-6-phosphate and then fructose-6-phosphate. Fructose-6-phosphate is converted to glucosamine 6-phosphate (GlcN6-P) by the

enzyme glutamine/fructose-6-phosphate-amido-transferase (GFAT). GlcN6P is further attached with glycosyl chain to modify the molecules of nucleus, cytoplasm, and cell membrane, resulting in altered cell function and cell injury. In fact, hyperglycemia induced activation of GFAT and glycosylation of crucial cellular proteins. When GFAT was inhibited by a specific inhibitor, glycosylation was suppressed and cell injury was prevented. Animals given glucosamine developed NCV delay and cultured neuronal cells exposed to glucosamine underwent apoptosis [28]. Since precise metabolic pathway of hexosamine is yet to be clear, role of this pathway in neuropathy is still unknown.

### *3.5.5 Oxidative Stress*

Oxidative stress has long been regarded as a main contributor to the pathogenesis of diabetic complications. In fact, its role in vascular complications or effect on endothelial cells or smooth muscle cells is well established by preclinical studies. There still remain many unsolved issues, however, on neurological complications in diabetes. There is a controversy on the source of oxidative stress. Recent studies disclosed decreased energy production (ATP production) in nerve mitochondria and less production of oxygen stress in diabetic nerve [15]. In Germany, based on the premise that oxidative stress is a major cause of neuropathy, alpha-lipoic acid, as an anti-oxidant, is clinically applied to the treatment of neuropathy. In short-term study, there was an improvement of subjective symptoms. No definite improvement was confirmed, however, by double-blind clinical trials; as such it is still not approved as an effective treatment.

### *3.5.6 Cytokine and Neurotrophic Factors*

There is an enhancement of inflammatory process in diabetic tissues. Also in the peripheral nerve, there is an increased infiltration of macrophages with excessive production of inflammatory cytokines. It was also found that TNF-α, IL-1α, and IL-1β were all increased in diabetic nerve where they affected the nerve as cytotoxic, thereby causing neurodegeneration [29]. Based on the data, TNF-α antagonist or cyclooxygenase (COX)-2 inhibitor was found to be effective for amelioration of experimental diabetic neuropathy in animals, but confirmation in humans is yet to be complete.

On the other hand, several studies demonstrated that production and release of nerve growth factor, neurotrophin 3, and ciliary neurotrophic factor (CNTF) were deficient in diabetic animals. Erythropoietin derivative was found to be effective for functional and structural deficits in animals with diabetes [30]. It is yet to be determined, however, whether the deficit of neurotrophic factors is the cause of neuropathy or merely the consequence of nerve damage in diabetes.

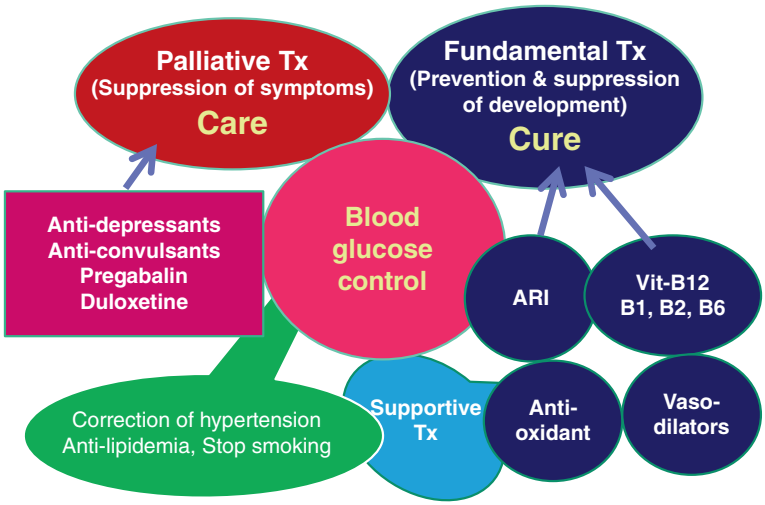


**Fig. 3.3** Management of diabetic neuropathy with consideration of "care" and "cure." The treatment of diabetic neuropathy should separately be considered to be "care" and "cure." For the relief of positive symptoms such as pain, drugs can be prescribed only as a relief. It should be of note, however, that such "care" does not prevent the progression of neuropathy. In contrast, fundamental treatment that attempts to halt the disease is based on the pathogenetic mechanisms. Since precise mechanisms are yet to be clear, multiple treatment regimens are required for the better management of neuropathy

## 3.6 Direction of Treatment

Final goal of diabetes treatment may be the maintenance of good quality of life and healthy life expectancy. To this end, it is essential to prevent the clinical onset of neuropathy and to inhibit the progression of symptomatic neuropathy. To achieve this goal, precise pathogenesis of neuropathy should be clarified to establish the fundamental treatment. For the management of diabetic neuropathy, care and cure should be separately taken into account (Fig. 3.3). Currently, there is no consensus on the treatment for the patients who already have an established neuropathy. To alleviate the symptoms, care is the main purpose, though palliative, in which pain control is the major problem. Recent development of analgesics or antidepressants improved the quality of pain control, but there still needs further development. In contrast to symptomatic therapy, means to prevent the progression or reversal of neuropathy is still immature. To develop effective treatment for the cure, clarification of natural history of neuropathy and establishment of appropriate clinical endpoint is crucial. Otherwise, candidate compounds based on the pathogenetic mechanisms may again be only effective for the animals, but not for humans.

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