Diabetic Neuropathy: Pathogenesis and Treatment

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INTRODUCTION

Diabetic neuropathy is a complication of diabetes mellitus that is often overlooked, since there are often no subjective complaints during initial stages, and sensory deficit is often only found after objective examination.

Diabetic neuropathy is defined by the San Antonio Concensus of 1988 as "clinical or subclinical neural disturbance that occurs in diabetes mellitus, with no signs of other peripheral neuropathy. Neuropathy may manifest on the somatic, peripheral, as well as autonomicic nervous systems."

The incidence rate of diabetic neuropathy is reported to be 10-90%. Such high variation is due to differences in the diagnostic criteria or method to establish the diagnosis.

Reports of peripheral neuropathy from various hospitals in Indonesia are as follows: Cipto Mangunkusumo Hospital / Jakarta (1989) 68.16%, Hasan Sadikin Hospital (1989) 12.2%, Dr. Sutomo Hospital / Surabaya (1990) 52.21%, Dr. Pirngadi Hospital / Medan (1996) 18.05%, Dr. Wahidin Sudirohusodo Hospital / Ujung Pandang (1997) 57.81%. Asril Bahar, Jakarta (1985), reported an incidence rate for parasympathetic autonomicic neuropathy of 11.9%, while Harsinen Sanusi, Ujung Pandang (1989) reported an incidence rate of 66.7%.

The duration of diabetes mellitus is associated with the incidence of diabetic neuropathy: the longer a patient has had diabetes, the more the chance od diabetic neuropathy.

Pirat reported an increasing prevalence rate of neuropathy in 4400 diabetes mellitus patients observed for more than 25 years, from 12% at the time of diagnosis to 50%.

Persistent hyperglycemia is the most important factor in the pathogenesis of diabetic neuropathy. If the patient's blood glucose is well regulated, the chronic complications of diabetes mellitus may be suppressed or inhibited. Pharmacological treatment has not come up with satisfactory results, and studies are continuously being conducted, and might shed light in the future.

CLASSIFICATION OF DIABETIC NEUROPATHY

There are many different classifications for diabetic neuropathy, depending on each author. One of them is as follows:

I. Distal Symmetrical Poly-neuropathy
   1. Sensory poly-neuropathy
   2. Autonomic neuropathy

II. Mono-neuropathy and Multiplex Mono-neuropathy.
   1. Cranial nerve lesion
   2. Peripheral nerve lesion
   3. Diabetic amyotrophy

Based on this classification, the most common condition is sensory poly-neuropathy, making up approximately 50%. This type of neuropathy occurs slowly and tends to be progressive in nature. Sensory disturbance begins in the feet (socks area) to the hands (glove area), arms, and finally to the abdomen and chest. During initial stages, this condition often does not produce subjective complaints, while objective signs may be found during examination in the form of sensory deficit.

In general, distal symmetrical poly-neuropathy is classified into 2 groups according to the nerve bundle, the large and small nerve bundles. Initial symptoms due to small nerve bundle neuropathy (nerve bundle C and A delta) may be negative as well as positive. Negative symptoms would be loss of pain and temperature sensation, which could create burns and wounds on the patient's feet without his/her realization. During advanced stages, the large nerve bundles may be affected, thus disturbing the sensation of vibration and position, thus making it difficult for the patient to maintain his/her balance, as if

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he/she is walking on a mattress, with reduced tendon reflex. Positive symptoms may take the form of sensations of heat, pain as if electrocuted, parasthesia, hyperalgesia, or allodynia. Generally, diabetic neuropathy takes the form of a combination between large and small nerve bundle disturbance, and rarely comes in one form only.

Motor disturbance occur at advanced stages, in the form of feet paresis (drop foot), paresis and atrophy of the intrinsic muscles, frequent tripping, and disturbed fine hand motion.

Autonomic neuropathy occurs in approximately 40% of patients who have had diabetes mellitus for over 10 years. Disturbance may occur on the sympathetic and parasympathetic nervous system. The parasympathetic system is more commonly affected than the sympathetic system.

Clinical manifestations of autonomic neuropathy may occur on the cardiovascular, gastrointestinal, or urinary systems; and may take the form of sudomotor disturbance, abnormal pupil response, and disturbance in neuroendocrine response. Symptoms may be hypotension, diarrhea, obstipation, nausea, disturbance in urinating, erectile dysfunction, or disturbance in sweating.

Longitudinal studies of autonomic neuropathy demonstrate a 5 year mortality of 16-53%, with the highest mortality rate due to cardiovascular disorder.

Cranial mono-neuropathy generally occurs acutely accompanied with pain. It may resolve spontaneously within 6-8 weeks. The cranial nerves that are affected are the 3rd, 4th, 5th, 6th, and 7th cranial nerves, the most common one being the 3rd cranial nerve.

Compression mono-neuropathy (entrapment) usually appears slowly and resides. The most common form is the Carpal Tunnel Syndrome due to compression of the median nerve. Aside from that, the posterior tibial nerve, the peroneus nerve, and the ulnar nerve may also be compressed. Surgical procedures are usually required. The prognosis is generally good.

Diabetic amyotrophy is often found in the elderly, appears suddenly or slowly, and may be unilateral or bilateral. Symptoms take the form of a jabbing pain in the hips and thighs, accompanied by paresis or atrophy of the leg muscle.

Radiculopathy is a rare form of neuropathy that is usually unilateral at the thoracic and upper lumbar regions. It may cause severe pain, a burning sensation, or hyperalgesia. It may affect one or more radix at once. The prognosis is usually good.

Neuroarthropathy (Charcot's joint) could cause symptoms of knee deformity, namely claw toe, due an imbalance of the extensor and flexor muscles. In addition to occurring due to neuropathy, it may also be a result of minor recurrent trauma and osteopenia.

Acute painful neuropathy could occur due to bad regulation of diabetes (blood glucose), undiagnosed diabetes, or an accelerated drop in blood glucose. Symptoms take the form of acute pain, burning sensation, and a sensation of being electrocuted. Symptoms usually appear at night, thus disturbing the patient's sleep.

PATHOGENESIS

Several factors that have been mentioned to play a role in the development of diabetic neuropathy are the metabolic factor, immune process, vascular process, and neurohormonal deficiency of growth factor. From these factors, the metabolic factor is considered to play the greatest role in the development of diabetic neuropathy. In poorly regulated diabetes mellitus, diabetic neuropathy could easily occur through 4 pathways: AGE, the polyol pathway, ROS formation, and PKC activation.

The Metabolic Hypothesis

Within several hours (under 24 hours), schiff base would be formed as a reaction between glucose and bodily proteins. This phase is known as Phase I and is still reversible in nature. Thus, blood glucose should be regulated to ensure a return to normoglycemia. In this phase, free radicals begin to form through auto-oxidation, and could already kill muscle cells as well as cells from other body tissues.

If blood glucose is not regulated in time (over 24 hours), Phase II takes place, where Amadori products are formed. These products are toxic to tissues, but the phase is still semi-reversible.

If hyperglycemia is prolonged (weeks, months, years), Advanced Glycation End-products (AGE) are formed. These products are very toxic and could destroy all kinds of body proteins, including nerve fibers.

Damage caused by this third phase may take the form of endothelial dysfunction, damage of blood vessels, nerves, and ischemia. Glucose auto-oxidation undergo catalization by a small number of metallic substances such as iron and zinc, forming Reactive Oxygen Species (ROS). ROS is closely associated with AGE, where ROS could increase AGE formation, while AGEs supply ROS. ROS could cause microvascular disturbances resulting in ischemia. In addition, ROS also suppresses neurotrophic support, thus reducing the capacity of the anti-oxidant system. If ROS formation exceeds the ability of the cellular mechanism to resolve it, involv-

ing a number of enzymes and anti-oxidant vitamins, a condition known as oxidative stress appears. In diabetes mellitus, there is an increase in ROS (superoxide anions, hydroxyl radicals, peroxynitrite, and hydrogen peroxide), while antioxidant capacity (superoxide dysmutase, catalase, glutathione, vitamin C, or vitamin E) is reduced.

Aside from auto-oxidation factors and AGE formation, the polyol pathway activity also plays a role in increasing oxidative stress.

Persistent hyperglycemia increases the activity of the polyol pathway, thus forming an accumulation of sorbitol and fructose in the nerves, which could destroy the nerve. Sorbitol deposit reduces the organic osmolarity of myoinocytol and taurine as endogenous antioxidants, thus reducing antioxidative capacity. A reduction of organic osmolarity accompanied by an increase in sorbitol directly causes osmotic stress, which destroys mitochondria and stimulates Protein Kinase C (PKC). Increased sorbitol also increases Diacylglycerol (DAG) which intern increases PKC activity. PKC is the one that suppresses Na^+ K^+ ATP-ase function, thus causing excessive amounts of intracellular Na+. This results in the inhibition of myo-inocytol entry into the cell, thus disturbing conduction. Both ROS and PKC causes microvascular dysfunction of peripheral tissues, which results in ischemia.

Due to the activation of the polyol pathway, there is an increase in fructose formation. Fructose would thus be metabolized into 3-phosphate fructose and triose phosphate, with 3-dioxyglycosone and methylglyoxal as end-products, which are AGE precursors.

Increased sorbitol reduces NADPH levels. NADPH is a co-factor for Nitric Oxide Synthase (NOS), which is very important for NO synthesis. As less NO is produced, is function is also reduced, thus reducing vasodilatation and blood flow to the nerve.

Oxidative stress and Reactive Oxygen Species are very potential components in the development of progressive dysfunction of neural fibers, severe neural damage, and destruction of axons in diabetic neuropathy.

The Immune Hypothesis

The presence of an immune process is supported by proof of circulating anti-neural antibodies that could directly destroy sensory as well as motor nerves and can be detected using indirect immunofluorescence. Anti-phospholipid antibodies (PLAs) is found in 88% of diabetes mellitus patients with neuropathy compared to 32% in diabetes mellitus patients without neuropathy and 2% in the general population. Another study found 12% of anti gangliocide antibodies (anti-G_{M1}) in distal symmetrical neuropathy. Since PLAs are associated with a ten-

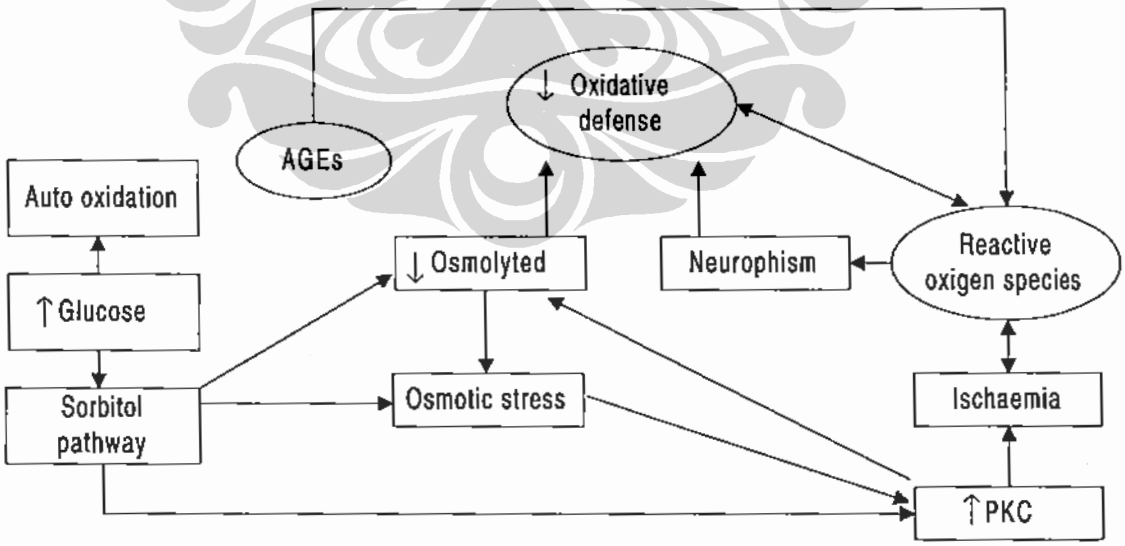

Figure 1. The Pathogenesis of Diabetic Neuropathy (Feldmann 2000)

dency for thrombosis formation, it is estimated that there is a relationship between the immune process and vascular theory in the etiology of neuropathy.

The Microvascular Hypothesis

Support for this hypothesis comes from a study that reports absolute or relative nerve ischemia due to functional changes in the endo- and epi-neural blood vessels.

Histopathologically, there are changes in the degree of damage in endo- and epineural blood vessels, in the fomr of thickening of blood vessel walls, even to the point of blockage. There is also reduced neural blood flow, increased vascular resistance, reduced O2 pressure, and changes in vascular permeability.

Growth Factor

It has recently been discovered that nerves require the Nerve Growth Factor (NGF) to encourage and maintain nerve growth. NGF is a family of genes that codes the form and structure of the protein Neurotrophin (NT).

A member of the neurotrophin family, NT3 for example, plays an important role in the growth of large neural fibers.

In this study, we found that decreased NGF synthesis in diabetes mellitus plays a role in the pathogenesis of neuropathy, particularly in fine nerve fibers that play a role in pain and heat sensations. In addition, IGF I and IGF II also influence nerve growth.

In cases of insulin deficiency, there is a reduction in IGF I, thus IGF deficiency may be considered as a cause of diabetic neuropathy.

Diabetic Neuropathic Pain

Pain that occurs in diabetes mellitus is caused by excitatory and inhibitory neurotransmitter imbalance. Several kinds of neurotransmitters that play a role in the process of pain are: serotonine, GABA, glutamate, P substance, and opioid peptide.

If the process of disinhibition such as GABA reduction, reduced opioid receptor function, or reduced descending inhibitory function such as serotonine and dopamine, there is increased excitation.

The pathogenesis of diabetic pain involves cellular and molecular processes. The presence of nerve injury/ lesions on the afferent nerve fibers through the C nerve fiber activation causes a release of Excitatory Amino Acids (EAAs). EAAx then activates N-Methyl-D-Aspartate (NMDA) receptors, which in turn increases intracellular levels of Ca++ and stimulates PKC activity while suppressing interneural inhibition, thus increasing the sensitivity of the dorsal horn neuron (see Figure 2).

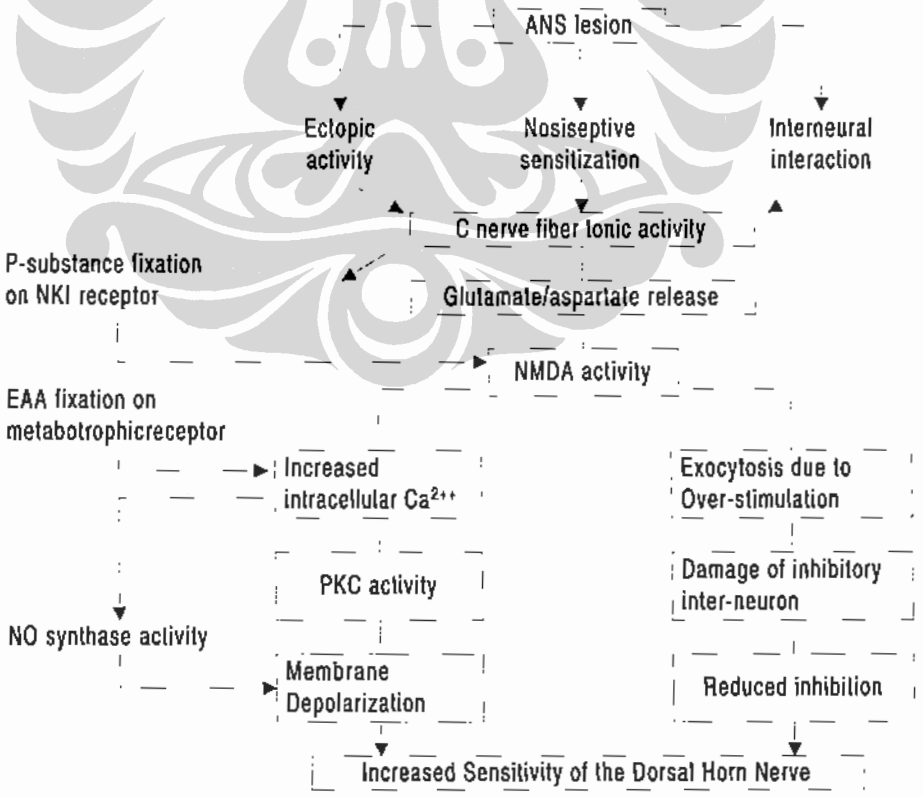

Figure 2. The Pathogenesis of Diabetic Pain (ATTAL 1999)

TREATMENT

Treatment for diabetic neuropathy consists of:

1. Blood glucose regulation
2. Pharmacotherapy
3. Foot treatment
4. Physiotherapy

Blood Glucose Regulation

Good and continuous blood glucose regulation is essential. Without it, each episode of hyperglycemia could cause the increase of the three main components causing diabetic neuropathy: the polyol pathway, increased AGE, and the production of free radicals.

Freports from DCCT state that intensive administration of insulin could significantly prevent the development diabetic neuropathy, reducing the incidence of neuropathy to 50% with intensive treatment for 5 years.

Intensive treatment mentioned here refers to maintaining preprandial blood glucose between 90-120 mg/dl, postprandial glucose to less than 180 mg/dl, and HbA1C to less than 6.05%. While according to UKPDS, intensive treatment maintaining HbA1C of 7% could suppress microvascular complication up to 25%.

Aldose Reductase Inhibitors (ARIs)

Even though up to now there is still no satisfactory results, ARI administration still has hope and is still being study.

This family of drugs inhibits sorbitol and fructose deposit in body tissues due to increased polyol pathway. The side effects of these drugs are lymphadenopathy, fever, rash, pancytopenia, and liver dysfunction. Drugs from this family that have been studied are alrestatin Tolrestat and sorbinil. These drugs were able to improve sensory and motor nerve conduction, even though the result was not considered significant, and in its development significant side effects were found.

These drugs have not been approved for use in the United States, and have solely been used in studies.

Gangliocides

Gangliocides are cyalo-glycolipids, which are the chief components of cell membranes. Several studies report that the administration of gangliocides may improve sensory and motor nerve conduction.

Gamma Linoleic Acid (GLA)

Patients with diabetes mellitus cannot change linoleic acid into GLA, a precursor for phospholipid membrane. Several studies in Europe reported that one-year GLA administration with a dose of 360-480 mg/day could improve sensory and motor nerve conduction.

Aminoguanidine

Drugs from this family inhibit AGE formation. Studies limited to rats demonstrate that aminoguanidine is able to improve nerve conduction and increase endoneurial blood vessel flow after 8 weeks of treatment.

The Action II trial comparing aminoguanidine and placebo in neuropathic and retinopathic regression in type 2 diabetes mellitus has not bben published.

Human Intravenous Immunoglobulin (IVI g)

Studies with this drug are based on the presence of the anti-neural autoimmune process. This drug can be used in combination with prednisone and azathioprine. The threatening side effect is anaphylactic reaction.

Neurotrophic Agents

In studies on animals that were made to have diabetes, there is a reduction of Nerve Growth Factors (NGFs) and Tyrosynkinase Transmembrane Protein (TrKA). Administration of recombinant NGF turned out to improve sensory neuropathy. The last reports from 15 research centers on 250 patients with diabetic neuropathy who received recombinant NGF demonstrated satisfactory results.

A dose of 0.3 mg/kg/subcutaneous recombinant NGF per week for 6 months (1-3 times/week) appeared to improve sensitivity to heat and cold. The side effect was hyperalgesia at the injection site.

A diet containing 3.2 g of inocytol and 500 g of Dihomo gamma linnoleic acid administered for 6 months also demonstrated satisfactory results.

Other treatment is aimed towards increasing blood flow through the vasa nervorum. Such drugs include prostacycline analogs, thromboxane A_2 blockers, and drugs that supposedly improve Na^+, K^+, ATPase activity, such as cyllostazole, phosphodiesterase inhibitor, and antioxidants.

Several new drugs that are being studies for diabetic neuropathy are recombinant C peptide for chronic complications of diabetes mellitus including diabetic neuropathy, and PKC inhibitor (Calphostin C) for diabetic pain. ACE inhibitor is an old drug that turns out to also improve nerve conduction.

VINIK (1999) found the pathogenesis pathway of diabetic neuropathy as well as possible intervention that could be achieved in each level (Figure 3).

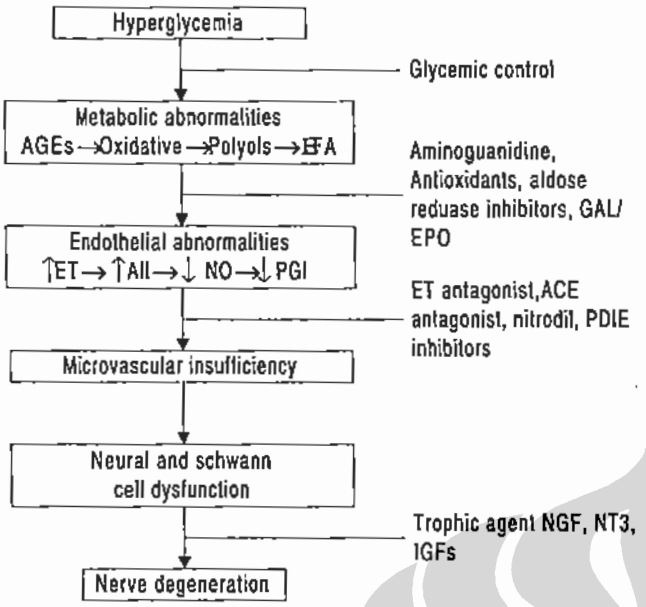

Figure 3.

Treatment for Diabetic Neuropathic Pain

Pain control in diabetic neuropathy is a fairly difficult problem for both the doctor and patient. Patients often feel depressed, which aggravates their sensation of neuropathy.

Treatment for diabetic pain is symptomatic in nature, aimed to alleviate pain. The drugs are chosen by taking into consideration the level of pain, the presence of accompanying symptoms, as well as the drug's pharmacological characteristics.

The types of drugs that can be used are as follows:

1. Non-steroid analgesics
   This type of drugs is administered for pain due to complications on the joint (neuroarthropaty) or musculoskeletal system.
2. Adjuvant analgesics
   Adjuvant analgesics are drugs that are not indicated for pain, but are able to alleviate neuropathic pain. Drugs that belong in this category are: anti-depressants, anti-convulsants, local anesthesia/anti-arrhythmia, corticosteroids, muscle-relaxants, neuropleptics, and topical drugs such as Lidocaine, Capcaisin, and Euthetic Mixture of Local Anesthetics (EMLA).

Antidepressants

The mechanism of action of tricyclic anti-depressants is by inhibiting the reuptake of serotonine and norepnephrine. Several studies demonstrate a better effect if tricyclic anti-depressants are administered along with phenothiasine or fluphenazine.

The dose of amitriptilline ranges from 50-150 g, administered in combination with 1-2 mg of fluphenazine. It has been reported that use of a nocturnal dose of 150 g of Amitriptillin significantly reduces the intensity of pain.

Common side effects include dysautonomy, dry mouth, sleepiness, and constipations. Other types of anti-depressants include nortryptillin, dysopiramine, and paraxetine.

Anticonvulsants

These drugs are able to reduce hyperexcitability and neural hyperactivity through various mechanisms depending on the type of drug.

The family of drugs that block Na channels are phenytoin, carbamazepin, and valproic acid, while those that increase GABA levels include clonazepam, gabapentine. Drugs that inhibit NMDA receptors are carbamazepone, phenytoin, while valproic acid inhibits calcium channels.

Local Anesthesia/Antiarrhythmic Agents

The mechanism of action of drugs from this group is by inhibiting sodium channels, thus reducing ectopic impulse from damaged peripheral nerves. A drug that belongs to this group is lidocaine, to be administered at a dose of 2-5 mg/kg bodyweight for 30 minutes per infusion. Mesylletine is administered orally with a dose from 150 g/day to 600-900 g/day.

Gabapentine has a rapid effect and is tolerable. Its mechanism of action is by increasing GABA metabolism by binding with GABA receptors, as well as by affecting Ca-channels.

Capcaisin is an extract from red chilli peppers, used topically. It inhibits pain through the P substance neurotransmitter of the peripheral sensory nerve fibers (type C). Its side effects are erythema and burning sensations.

Feldman (2000) summarized treatment for diabetic neuropathy (see Table 1)

According to Feldman (2000), superficial pain with burning sensations may receive 0.25-0.75% of Capcaisin cream 4 times daily at the site of pain. Deeper pain, such as jabbing sensations, should receive gabapentine or tricyclic antidepressants in combination with mexyletine or local anesthesia (lidocaine). Muscle pain should receive muscle relaxants or NSAIDs.

Autonomic Neuropathy

Treatment of postural neuropathy is quite a problem. Administration of 0.5 mg/day of 9-fluorohydrocortisone and a high sodium diet may be used

Table 1.

1	NSAID
	Ibuprofen 4 x 600 mg
	Sulindac 2 x 200 mg
2.	Tricyclic anti depresan
	Ami triptylin 50 – 150 gr/bedtime
	Nortriptylin 50 – 150 gr/bedtime
	Imipramine 100 mg/daily
	Praxetine 40 mg/daily
3.	Analgetic Non Addictive
	Carbamazepine 4 x 200 mg/daily
	Gabapentin 3 x 900 mg/daily
	Mexiletine 150 – 450 mg/daily
4.	Others
	Capsaicin : 0,75% 4 x once day
	Fluphenazine 3 x 1 mg /daily
	Transcutaneous Nerve Stimulation (Tens)

for treatment of postural hypotension, even though it increases the risk of heart failure and hypertension. If this is not successful, 10 mg of metoclopramide 3 times a day may be used to increase sensitivity to dopaminergic stimulation.

Midodrine, which is an alpha 1 adrenergic agonist, could be administered at a dose of 2.5 to 40 mg in combination with caffeine (cafergot) for postural hypotension.

Refractory post-prandial postural hypotension may be treated with subcutaneous Octreotide (Sandostatin) at a dose of 0.1-0.5 mg/kg bodyweight in the mornings. Body stocking could also be used to increase venous return, used when lying down and not removed until the patient returns to a standing position.

For gastroparesis, small, frequent meals are recommended, most preferably gluten-free. Be careful with high fiber diets, since bezoars may be form in diabetic neuropathy due to bowel stasis, gastroparesis, and constipation. Metoclopramide at a dose of 4 times 10 mg/day may be administered. Other drugs, such as bethanicol (a cholinergic agent), cisapride, and domperidone (10-40 mg) may be administered 30 minutes prior to meals. Erythromycin may be administered in fluid or suppository form, since it has an effect on motillin receptors that shorten gastric evacuation time.

Diarrhea in diabetes may be caused by various reasons. If bacterial growth due to bowel hypomotility is suspected, 3 x 250 mg of Tetracycline or 4 x 500 mg of metronidazole may be administered.

Cholestyramine may be administered if bile retension irritates the bowel. Bladder incontinence may be treated with parasympatomymetics such as bethanicol, alpha blockers, or 1-2 mg of doxasosine 3 times daily as a sphincter relaxant. Bladder neck surgery may be performed if the drugs are not successful.

Several drugs for erectile dysfunction, such as adrenergic antagonists (johimbin, mynoxidil), intrapenile injection of papaverine, and prostaglandin E may be administered. Papaverine injection may cause priapismus, fibrosis, or infection. The newest drug is Sildenafil citrate (Viagra), a cyclic GMP phosphodiesterase inhibitor that may be administered for all forms of erectile dysfunction. Sildenafil citrate was reported to have a success rate of approximately 44% in patients with diabetes mellitus. The use of vacuum instruments or prosthetic penile devices should be considered based on the patient's needs.

Gustatory sweating and sudomotor disturbances may be treated with 15 mg of propantheline hydrobromide 3 times daily.

In autonomic neuropathy, hypoglycemia may occur without the patient's awareness due to unclear symptoms. For this, blood glucose or HbA1C reduction to normal levels is not recommended.

Foot Treatment

Foot treatment is a part of the primary prevention effort for diabetic foot management, aimed to prevent the development of wound. Each foot should be examined every time for wounds, and the feet should be cleaned with clean water and dried particularly between the toes, and moisturizing lotion should be used except between the toes. Recurrent trauma from tight-fitting shoes should be avoided.

Foot exercises could improve blood circulation and strengthen feet muscles to prevent small muscle disorder.

Physiotherapy may be conducted in the form of massage, muscle relaxation exercises, and pain treatment using transcutaneous nerve stimulation (TENS), as well as shortening the time of inactivity to prevent further complications.

CONCLUSION

1. Diabetic neuropathy is a complication of diabetes mellitus with a high incidence rate but is often overlooked by health providers.
2. Sensory polyneuropathy is the most common form of diabetic neuropathy.

3. There are many theories that attempt to explain the pathogenesis of diabetic neuropathy, but the metabolism theory is still the main pathogenesis.
4. Continuous blood glucose regulation is essential in the treatment of diabetic neuropathy. Symptomatic treatment is rendered most appropriate, since there is no single drug that has been proven to be truly effective for diabetic neuropathy.

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