Chapter 20 Pathobiology of neuropathy

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SUMMARY

- A wide variation in the reported prevalence and incidence of diabetic neuropathy results from the many differences in defining the condition, the tests used to assess it, and the patient population under consideration
- In addition, there are considerable differences in the interpretation of the various tests used to determine the presence or absence of neuropathy
- Diabetes-related neuropathy can have serious adverse effects on a wide variety of normal body function
- Motor nerve dysfunction results in disturbances in posture and balance that can, in turn, lead to increased pressures within the foot
- Loss of sensory perception results in an inability to feel trauma that would have otherwise resulted in pain, thus inhibiting any early preventative action from being taken
- Loss of autonomic function in the lower limbs leads to a loss of sweating and hence very dry skin. This, in turn, leads to an increased risk of the skin cracking, allowing the entry of pathogens into the wound
- Autonomic dysregulation also disrupts the ability to control vascular blood flow
- It is extremely difficult to get accurate estimates of the incidence and prevalence of neuropathy
- The most important factors that determine the development of the condition are poor glycemic control and increasing duration of diabetes
- There remains debate over the exact pathological mechanisms that are responsible for the development of diabetic neuropathy

INTRODUCTION

In 1864, Marchal de Calvi first recognized that diabetes affect the nervous system (de Calvi 1864), but it was not until 1885 that diabetic polyneuropathy was first described (Pavy 1885). Pavy described many of the classic symptoms of hyperesthesia or anesthesia, as well as the loss of tendon reflexes. However, due to the lack of technological capability in the late 19th and early 20th centuries, it was not until 1945 that the first comprehensive description of autonomic neuropathy appeared (Rundles 1945). It was this same lack of technology, and the lack of formal definitions of neuropathy that have led to the delay in getting robust data on the incidence and prevalence of neuropathy in the diabetes population. The different rates of nerve fiber population involvement mean that it is often difficult to differentiate types of neuropathy. Furthermore, the long follow-up needed for a large number of patients whose glycemic control varies over time mean that, until recently, there are very few reliable data on neuropathy in people with diabetes; moreover, only in recent years it has become clear that nerve conduction slows with age even in those without diabetes.

Given the recognition that diabetes has been associated with peripheral neuropathy, regular foot examination, checking for loss of protective sensation, has long been part of the standard of care for people with diabetes. Examinations starting from the time of diagnosis for people with type 2 diabetes and after 5 years of diagnosis for those with type 1 diabetes have been advocated (American Diabetes Association 2013). An understanding of the pathobiology of neuropathy is important because of its strong association with premature cardiovascular death (Coppini et al. 2000, Forsblom et al. 1998). The association with several modifiable risk factors for cardiovascular disease means that the presence of neuropathy should prompt early and aggressive treatment to optimize these risk factors. However, there is debate about how neuropathy should be diagnosed.

There are numerous classifications of diabetic neuropathy based on clinical features, etiology, anatomical patterns, or pathogenesis. The classification originally proposed by Thomas (1997) has been advocated by the American Diabetes Association and other expert groups (Boulton et al. 2005, Tesfaye 2010). The condition that is termed 'neuropathy' is a heterogeneous group that varies by symptoms, underlying mechanisms, and patterns of neurological involvement (Dyck et al. 1993). In essence, neuropathy can be classified as motor or sensory, or large fiber or small fiber. Small fiber neuropathy often precedes large fiber disease and is manifest by the classic symptoms of pain, numbness, and loss of pinprick and light touch perception. The large fiber neuropathy results in the loss of vibration sense and muscle weakness, with loss of tendon reflexes. It is, however, rare to get isolated small or large fiber symptoms or signs, with most patients exhibiting a mixed picture.

THE ANATOMY OF THE PERIPHERAL NERVOUS SYSTEM

Briefly, the nervous system is divided into three main components – motor, sensory (together known as somatic nerves), and the autonomic nervous system. Each of these systems has a vital role to play in the development of diabetes-related foot disease. **Figure 20.1** shows a cross section of the thoracic spinal cord highlighting the major ascending and descending pathways.

Motor nerves

The motor nerves descend from the brain in a variety of specialized anatomical pathways, including the lateral corticospinal and rubrospinal tracts that carry the nerves responsible for voluntary movement. The ventromedial pathways includes the reticulospinal tract, which is primarily responsible for locomotion and posture, and the tectospinal and vestibulospinal tracts, which are responsible for control of movement within the head and neck.

Once the nerves have made connections with the peripheral motor nerves in the ventral horn of the spinal cord, the motor neurons then progress to skeletal muscle. The myelinated α-motoneurones form the major bulk of these peripheral nerves and end on skeletal muscle fibers in a motor end plate. The number of motoneurons per muscle fiber determines how fine the resultant movement should be. The more precise a movement, the fewer motor neurons it has. The constant low-grade ('background') activity of these motor nerves also maintains the

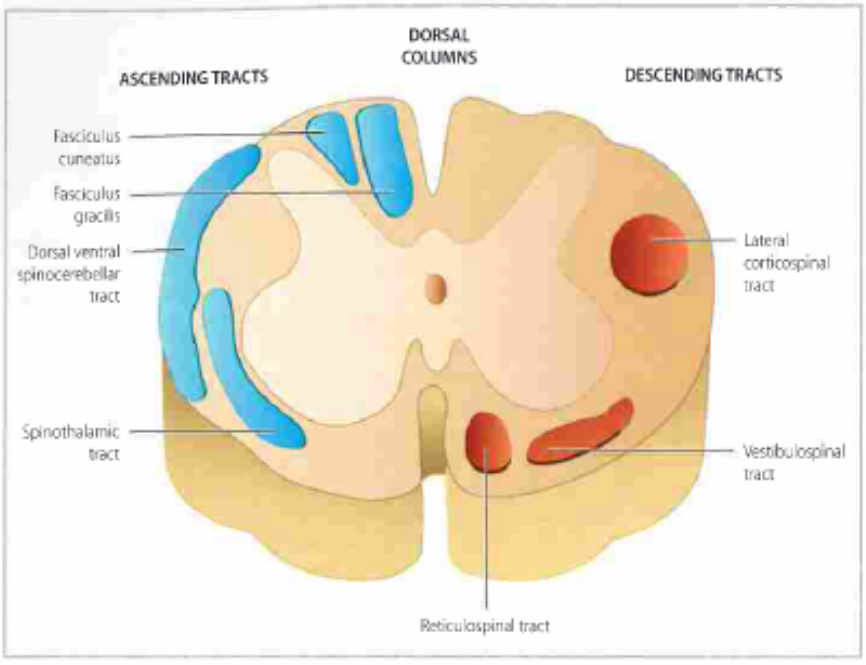

Figure 20.1 A cross section through the spinal cord at the thoracic level showing the major ascending (blue) and descending (red) tracts.

integrity of the muscles. This means that the muscles are constantly being stimulated and their strength maintained.

Sensory nerves

These nerves, often called the somatosensory nerves, bring nerves impulses from the periphery to the spinal cord and from there to the sensory areas within the cerebral cortex. The two main pathways within the spinal cord are the dorsal columns, which carry information about touch and proprioception, and the spinothalamic tracts, which convey information on pain and temperature.

There are three different forms of sensory receptors that relay information from the outside world into electrical impulses. These are the mechanoreceptors, which respond when they are moved (e.g. when a muscle changes position) or deformed under pressure. Thermoreceptors detect changes in temperature and nociceptors that detect stimuli, which would, under normal circumstances, be associated with tissue damage and is thus painful.

Together, these motor and sensory nerves make up the peripheral nerve fibers. Within these fibers are nerves of varying diameter - with all but the finest nerves being myelinated. The larger the diameter of the nerve, and the more associated myelin, the faster the nerve conduction velocity. The Aα fibers are the largest, ranging from 8 to 20 μm in diameter with a conduction velocity of between 44 and 120 m/s. The Aγ fibers that make up the motoneurons to individual muscle spindles have less myelin and are smaller in diameter than the Aα fibers, with a diameter of 3–8 μm and a slower conduction velocity of 18–48 m/s. The finest nerves are those without any myelin cover and thus have the slowest conduction speed. These are the C fibers associated with warmth and pain sensation with a diameter of <1.5 μm and a conduction velocity of 0.5–2 m/s. It is these thinnest fibers, which are often found furthest away from the central nervous system that is usually (but not always) affected first by diabetes.

Autonomic nerves

The autonomic nerves are integral to maintaining normal functioning in almost every organ in the body. They are vital to maintaining homeostasis. It is divided into the sympathetic and parasympathetic systems. The sympathetic nerves leave the spinal cord at all thoracic levels innervating many organs from the eye, the salivary glands to the heart, major abdominal organs, adrenal glands, and blood supply. It also innervates the bladder and reproductive organs. The parasympathetic nervous system leaves the central nervous system along several cranial nerves (III, VII, IX, and X) and through these innervates the eye, the salivary glands, the lungs and heart, and several major abdominal organs. The parasympathetic nerves also leave the sacral spinal cord to innervate the large bowel, the bladder, and reproductive organs. The long intra-abdominal path of the vagus nerve means that when this is affected, then gastrointestinal symptoms, such as early satiety, nausea and vomiting, constipation, and bloating, are more common.

The autonomic nervous system has several functions within the cardiovascular system. It regulates heart rate and allows the maintenance of blood pressure by maintaining vasoactive tone as well as sensing circulating blood volume in the baroreceptors. It controls the rate of transit of food from be oropharynx to the rectum. The parasympathetic nervous system in men is responsible for penile vasoconstriction, allowing an erection to be sustained, whereas the sympathetic system controls ejaculation. The skin is heavily innervated to allow for adequate thermoregulation, with the autonomic nervous system controlling peripheral vasodilatation and vasoconstriction, and sweating. Autonomic neuropathy leads to a loss of sympathetic constrictor tone. In the feet, this is typically associated with peripheral vasodilation and increased thermoregulatory blood flow, resulting in a relative warm foot with distended veins. However, if an injury occurs, there is an inability to allow for further vasodilation, leading to a 'relative reduction' in the necessary perfusion to allow

for adequate wound healing. This is discussed later in this chapter. The presence of autonomic neuropathy is associated with a poor prognosis, with previous estimates of 2.5-year mortality being 44% (Ewing & Clarke 1982).

TESTING FOR NEUROPATHY

Although this is dealt with in more detail in the next chapter, one of the reasons for the wide variation in reported prevalence and incidence of diabetic neuropathy have been the many differences in defining the condition, the tests used to assess it, and the patient population under consideration. In addition, there are considerable differences in the interpretation of the various tests used to determine the presence or absence of neuropathy (Dyck et al. 2010). As a result of these findings, it is important for the clinician to choose a small set of tests designed to assess different modalities of sensation and stick to them. For example, tests to assess vibration perception could include a 128-Hz tuning fork or a neurothesiometer. It has been shown that in individuals who have a vibration perception threshold of ≥ 25 Hz have a greater than eightfold increase of developing ulceration (Young et al. 1994). Combinations of tests have been shown to have >87% sensitivity for detecting peripheral neuropathy (American Diabetes Association 2013). While outside the remit of this chapter, testing for evidence of peripheral vascular disease is also an integral part of the foot examination.

THE CONSEQUENCES OF NERVE DAMAGE IN THE LOWER LIMBS AND FEET

With these many functions in mind it can be seen that diabetes-related neuropathy can have serious adverse effects on a wide variety of normal body function. However, because this insidious condition tends to affect the longest axons, it is the feet that are affected first before proximal progression affects the hands. It is also usually the case that sensorimotor neuropathy becomes symptomatic before autonomic neuropathy. With respect to the feet, several different interactions come together to create potential problems.

Consequences of motor nerve dysfunction

As mentioned, the motor nerves are responsible for maintaining normal posture and balance. With the loss of neuronal activity, posture and balance diminish, leading to increased pressures within the foot in an attempt to maintain posture and balance.

In addition, the small muscles of the feet lose their strength due to the loss of the background neuronal activity. Due to the differential loss of strength between the extensor muscles and the flexor muscles, the extensors remain stronger than the flexors, and toes often become clawed. As illustrated in **Figure 20.2**, over time, this is thought to lead to the toes often dislocating, exposing the heads of the metatarsals. The head of the metatarsals are then pressing directly on the deeper skin structures. As a result, the shear stresses on the skin under the metatarsal heads increase, as the direct pressures are likely to increase the load over a smaller area. However, given that the toes also claw, the pressure distribution also becomes concentrated on the tips of the toes, resulting in higher pressures during the gait cycle. Thus, pressure ulcers can develop in a variety of sites across the foot.

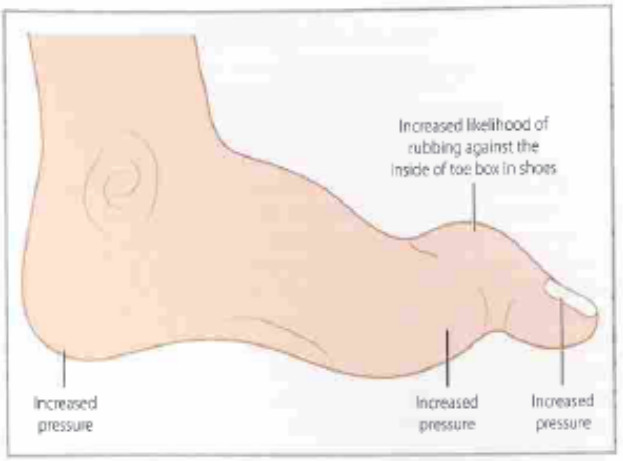

Figure 20.2 The shape of the foot with motor nerve dysfunction. The characteristic 'clawing' is due to the differential loss of strength between the extensor muscles and the flexor muscles leading to areas of high plantar pressures and an increased risk of the dorsal aspects of the toes rubbing against the inside of the toe box of a shoe.

It is at this stage that patient education is paramount, so that they are aware of their risk and take appropriate preventative action. This includes using correct foot wear to correctly redistribute the abnormal plantar pressures with the use of appropriate insoles and other pressure relieving devices. Without these, the increased pressures often lead to callus formation and ultimately lead to an increased risk of ulceration.

Consequences of sensory nerve dysfunction

The most obvious result of the loss of sensory perception is the inability to feel trauma that would have otherwise resulted in pain. This loss of sensation then results in preventative action not being taken (e.g. stepping on a pin and not feeling it). This often results in the protective barrier offered by the skin being breached and entry of pathogens into the subcutaneous tissues and infection ensuing.

The loss of protective sensation also means that in instances where the foot is in some way damaged (e.g. twisting an ankle) then that pain is not felt, and gait is not altered to allow healing of that area. In people with intact sensation, a person may limp, or keep their weight of the injured area; however, in neuropathy this does not occur, resulting in ongoing trauma to the injured area – making it worse.

The loss of proprioception means that the individual does not know where their foot is at any given time. This will eventually result in the classic 'high stepping' gait associated with a distal peripheral neuropathy. This results in abnormal pressure distributions on the plantar surface of the foot when it is put on the floor. Due to the sensory loss in combination with the motor dysfunction and loss of muscle strength, patients with diabetic neuropathy can have an abnormal and unstable walking pattern, with an increased tendency to fall. The postural instability and these spatiotemporal changes in gait are important, but frequently unrecognized, factors in the loss of quality of life in these patients.

Figures 20.3 and **20.4** show the consequences of distal symmetrical large fiber and small fiber polyneuropathy.

Consequences of autonomic nerve dysfunction

Loss of autonomic function in the lower limbs has two main consequences. First, sweating is important to maintain moisture within the skin. The loss of autonomic function leads to a loss of sweating and hence very dry skin. This leads to an increased risk of the skin cracking and allows the entry of skin organisms into the wound.

The other main effect of autonomic dysregulation is the loss of the ability to control vascular blood flow. If an injury occurs and the underlying tissues are exposed, then a variety of mechanisms lead to vasodilatation to encourage an increased blood supply to the site of injury. The immediate response to an injury is to vasoconstrict the surrounding blood vessels to stem the flow of blood loss, but very soon afterward, the blood flow increases to allow the materials in the blood that would heal the wound to be delivered more swiftly. Apart from local mediators, the autonomic nervous system allows for further vasoconstriction and then vasodilatation to occur. However, in autonomic neuropathy, these changes in blood flow do not occur. There is a loss of vasoconstriction and a loss of vasodilatation. These changes are thought to contribute to an impairment of wound healing.

EPIDEMIOLOGY

It is extremely difficult to get accurate estimates of the incidence and prevalence of neuropathy. Older data suggested that the annual incidence of neuropathy was between 2% and 3% (Partanen et al. 1995, Pirart 1978, UK Prospective Diabetes Study [UKPDS] Group 1998) and was the same for people with type 1 and type 2 diabetes (Young et al. 1994). A 1993 study suggested that the overall prevalence of neuropathy in 119 diabetes centers from around the United Kingdom was 28.5% (Young et al. 1993). The incidence increased with duration of diabetes, with 36.8% of the population having a diagnosis of neuropathy if diabetes had been present for ≥10 years. In addition, age was an important factor, with 44.2% of patients aged between 70 and 79 years being affected. These data are consistent with the 30–40% prevalence reported from other populations (Fedele et al. 1997, Tesfaye et al. 1996). Despite these data, the actual incidence may have been different, given that the vast majority of diabetes care was provided in the community most of whom are less likely to have complex diabetes-related end-organ damage than a secondary care population (Walters et al. 1992a). Further difficulties arise when one considers the large numbers of people with diabetes who remain undiagnosed (Walters et al. 1992b). In addition, given the difficulties on defining diabetes-related sensorimotor neuropathy, it is hard to get good estimates of prevalence (Dyck et al. 2010). However, some newer data have suggested that the prevalence of painful diabetic polyneuropathy in the community is approximately 16–26%. Quality of life is reduced in patients with painful neuropathy, with restrictions in the activities of daily living and social activities. In addition, painful neuropathy is associated with sleep disturbances, anxiety, and depression (Jude & Schaper 2007). These difficulties in diagnosing

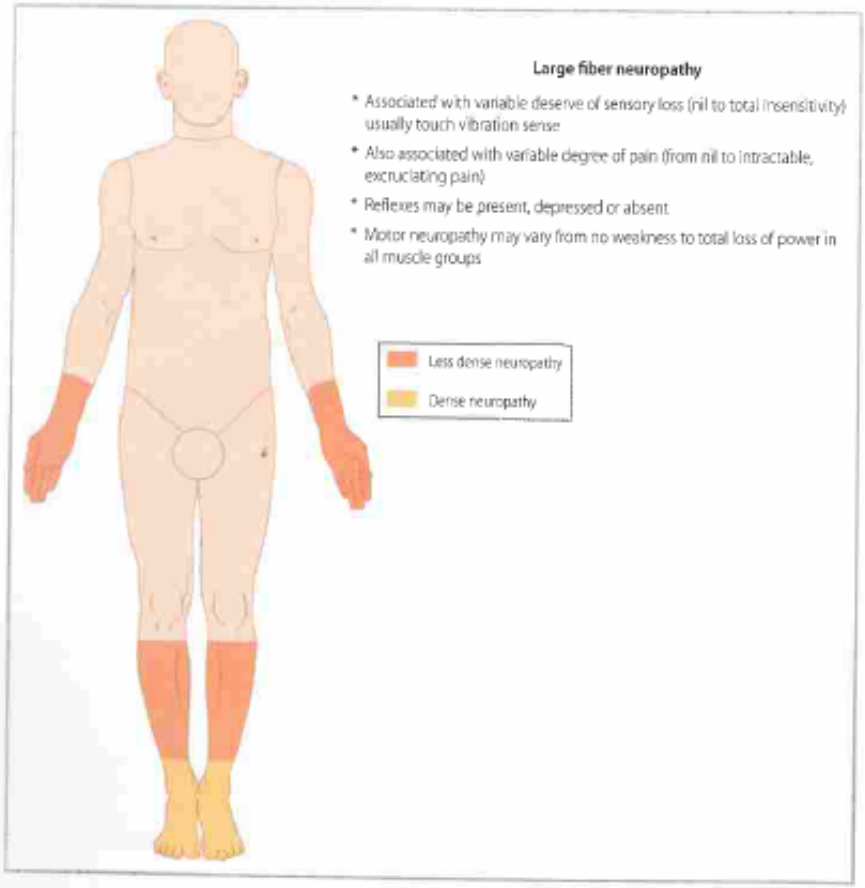

Figure 20.3 The 'stocking and glove' distribution of the sensory defect seen with large fiber neuropathy.

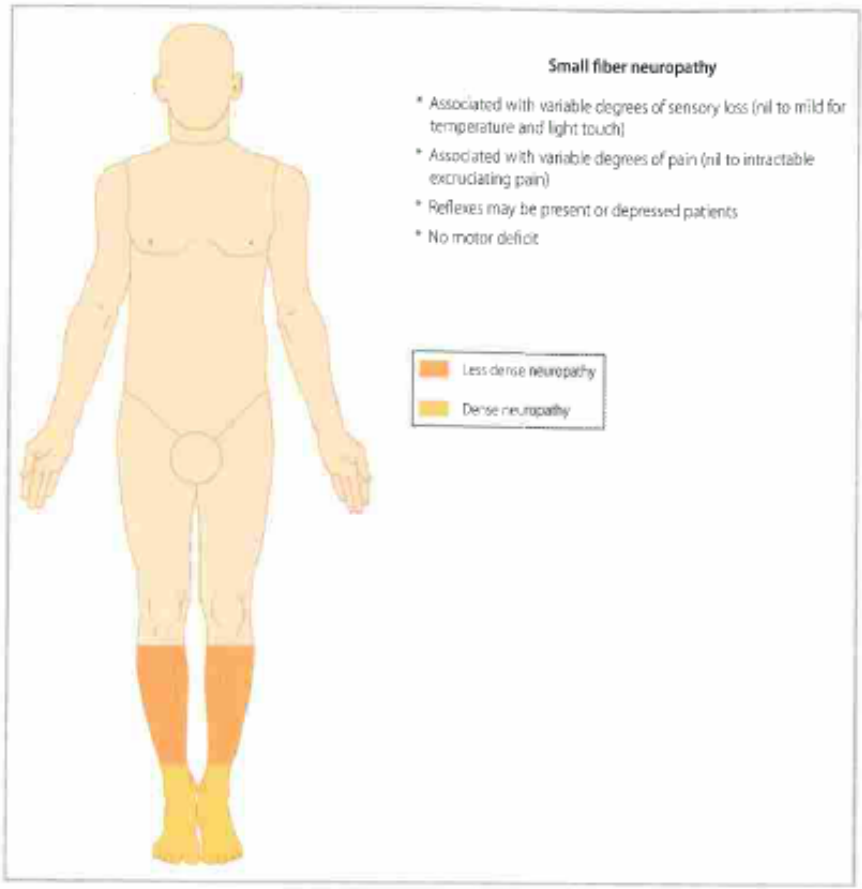

Figure 20.4 The distribution of the sensory defect seen with small fiber neuropathy. There is an overlap with the abnormalities seen with large fiber neuropathy, but clinical examination shows different neurological modalities being affected.

or defining neuropathy are further highlighted when considering the Diabetes Control and Complications Trial (DCCT) cohort. According to the theories about long-term chronic hyperglycemia, people with type 1 diabetes within 5 years of diagnosis should not develop a chronic complication; however, between 0.3% and 21.8% of that population had a degree of neuropathy, depending on the definitions used (The DCCT Research Group 1995).

In summary, the available data suggest that despite the improvements in controlling hyperglycemia, the prevalence of peripheral neuropathy remains high, with many people either not diagnosed correctly or not treated appropriately. It may well be that in the intervening years with the publication of the DCCT and the UKPDS, that as overall glycemic control of people with diabetes has improved, so the incidence and prevalence of diabetic neuropathy has declined (The DCCT Research Group 1993, UKPDS Group 1998).

DIFFERENTIAL DIAGNOSIS OF A DISTAL SYMMETRIC POLYNEUROPATHY

The differential diagnosis of distal symmetric polyneuropathy is large and is listed in **Table 20.1**. As with most conditions, a 'pathological sieve' should be used to exclude other causes.

PATHOLOGICAL MECHANISMS

Over the last few years, several metabolic, immune, microvascular, and neuroendocrine factors have emerged as contributing to the development of peripheral diabetic neuropathy. However, it has been recognized for several decades that the most important factors that determine the development of the condition are poor glycemic control and increasing duration of diabetes (Dyck et al. 1999, 2006, Pirart 1978).

There remains debate over the exact pathological mechanisms that are responsible for the development of diabetic neuropathy. Part of this comes from the DCCT data that showed that despite intensive glycemic control leading to a 60% reduction in neuropathy, the cumulative incidence or neuropathy remained high (15–21%), as did the cumulative incidence of abnormal nerve conduction (40–52%) (The DCCT Research Group 1995). These data suggest other factors may be responsible for the development of neuropathy in the face of tight glycemic control.

The DCCT data demonstrated that in those without neuropathy at baseline, but went on to develop it, there were statistically significant correlations with 'traditional' risk factors, such as HbA1c, age, duration of diabetes, body mass index, the presence of hypertension, microalbuminuria, retinopathy, and a history of cardiovascular disease (The DCCT Research Group 1995). Observational data of >1100 patients have shown that a change in glycemic control

Table 20.1 Some of the more common causes of distal symmetric polyneuropathy. As always, a good history and physical examination will help narrow down the differential diagnosis

Metabolic or endocrine	Diabetes mellitus
	Uremia
	Vitamin B12 deficiency
	Hypothyroidism
	Porphyria
Malignancy	Paraneoplastic syndromes
	Amyloid
	Myeloma
Vascular	Vasculitis
Congenital/familial	Charcot–Marie–Tooth disease
Trauma	Entrapment neuropathies
Inflammatory or infection	Sarcoid
	HIV
	Leprosy
	Syphilis
	Borrelia infection (Lyme disease)
Autoimmune	Type 1 diabetes mellitus
	Antiphospholipid/anticardiolipin syndrome
	Guillain–Barré syndrome
	Chronic inflammatory demyelinating neuropathy
Toxicity	Alcohol
	Chemotherapy
	Heavy metals

was associated with a change in risk of subsequently developing neuropathy over 7 years of follow-up. These authors found that with a rise in HbA1c of 16.3 mmol/mol (1.9%), the odds ratio of developing neuropathy increased by 2.48 (95% confidence interval 1.5–4.11) (Tesfaye et al. 2005). Although one study has shown a relationship between height and the risk of developing neuropathy (Gadia et al. 1987), other studies have found that there were significant associations with less established, potentially modifiable risk factors that remained significant after adjustment for the improvement in HbA1c over the duration of the trial. These included smoking, high levels of total cholesterol, low-density cholesterol and triglycerides, and low levels of high-density cholesterol (Maser et al. 1989, Mitchell et al.1990, Tesfaye et al. 2005, The DCCT Research Group 1995). What is less contentious is that it is thought that the chronic hyperglycemia leads to intracellular damage, much of which is probably reversible in the early stages of the condition, but that over time, becomes irreversible. Animal studies suggest that hyperglycemia affects several metabolic pathways, each with their own downstream pathways being affected. Thus, research has been focused on learning many of these pathways to see if anything – other than improving glycemic control – can be done to detect pathological changes early and if these changes can be prevented or reversed. Given that these irreversible changes occur before neuropathy is clinically detectable, this makes intervention and treatment very difficult indeed. However, it also gives further reasons (if any were needed) to ensure that glycemic control is held as close to the levels seen in people without diabetes as possible from the time of diagnosis for as long as possible.

Aldose reductase and the polyol pathway (Figure 20.5)

The oldest and perhaps best-known etiological hypothesis is the aldose reductase hypothesis (Brownlee 2001, Tomlinson & Gardiner 2008). Glucose entry into nervous tissue is independent of insulin and with increasing glucose concentrations aldose reductase is activated. Aldose reductase is the rate-limiting enzyme of the polyol pathway and is generally inactive when glucose levels are in the range of 3 to 6 mmol/L, because it has a low affinity for glucose. Glucose is preferentially metabolized by hexokinase, an enzyme with a much higher affinity for glucose, and rapidly transforms glucose into glucose-6-phosphate. When glucose levels rise in diabetes, the hexokinase pathway is saturated forcing more glucose down the sorbitol pathway where the enzyme aldose reductase converts the glucose to fructose via sorbitol using the enzyme sorbitol dehydrogenase. However, the conversion of sorbitol to fructose is very slow, leading to build up of sorbitol. This reaction uses nicotinamide adenine dinucleotide phosphate (NADPH) as a proton donor. However, NADPH is also used by glutathione reductase to convert reduced glutathione (GSH) to glutathione disulphide (GSSG). GSH is important because it removes hydrogen peroxide. The excessive use of NADPH by the sorbitol pathway results in lower levels of GSH and thus higher levels of hydrogen peroxide. The hydrogen peroxide is produced by normal mitochondrial respiration that produces free oxygen radicals that are themselves converted to hydrogen peroxide by superoxide dismutase. When levels of hydrogen peroxide build up, the Fenton reaction liberates the free radical superhydroxide that is damaging to the surrounding tissues (so called 'oxidative stress'). Thus, high glucose levels ultimately lead to a reduction in superoxide removal. It is these superoxide molecules that have been implicated in damaging strands of DNA. This, in turn, leads to reductions in intracellular NAD, thus slowing the rate of conversion of sorbitol to fructose, leading to a greater buildup of sorbitol. Sorbitol diffuses very slowly out through cell membranes, thus intracellular accumulation ultimately leads to irreversible cell damage and cell death.

Further damaging processes also occur as a result of high intracellular glucose. As mentioned above and shown in **Figure 20.5**, once the glucose is converted to glucose-6-phosphate, most of it is metabolized to fructose-6-phosphate. This molecule is metabolized in two main ways. First, fructose-6-phosphate is converted into glyceraldehyde-3-phosphate. This is metabolized into the highly damaging methylglyoxal. This molecule, as well as other reactive glucose metabolites, nonenzymatically attaches to other proteins, resulting in the accelerated formation of advanced glycation end products (AGEs) and so, cellular dysfunction. In addition, these proteins may extravasate, leading to progressive microvascular occlusion. Over time, as renal function deteriorates, AGE clearance is impaired, thus perpetuating the problem. AGEs can affect nerve function in two main ways. First, protein glycation affects structure and normal biological function. Second, the binding of AGE to cell surface receptors (RAGE) leads to activation of an inflammatory intracellular signaling cascade, increasing the oxidative stress.

The second pathway for fructose-6-phosphate is as a metabolite for the hexosamine pathway. This converts fructose-6-phosphate into uridine diphosphate-*N*-acetylhexosamine (UDP-GlcNAc). This molecule has an affinity for serine and threonine residues on proteins such as Sp1. This binding of UDP-GlcNAc to these proteins, in turn,

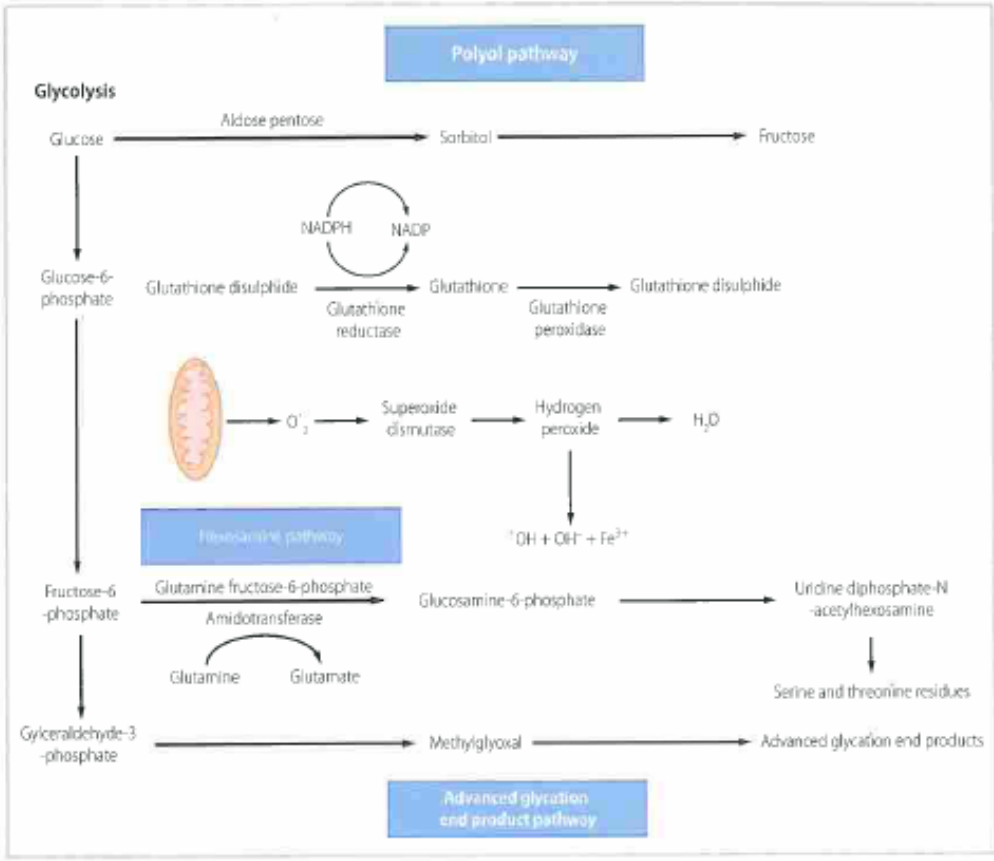

Figure 20.5 The aldose reductase and the polyol pathway showing the potential fate of glucose entering the cells. Please see text for a full explanation of the pathway.

adversely affects their structure and function and has been suggested as a contributory factor to the inflammation and endothelial injury seen in hyperglycemia.

The intracellular hyperglycemia and activation of the aldose reductase pathway described above is also associated with activation of intracellular signaling pathways mediated by the mitogen-activated protein kinases. These kinases are also activated by high levels of oxidized low-density lipoprotein (LDL) and RAGE. These molecules perform key roles in the intracellular signaling pathways, with at least two (p38 and JNK) being activated in the face of intracellular hyperglycemia. Activation is associated with phosphorylation of a variety of proteins, including ion channels, disrupting their function, and eventually causing measurable changes in cell damage and in nerve function.

With these multiple pathological mechanisms in mind, several agents have been tried to try and prevent the damage done by these processes. Aldose reductase inhibitors have been used, as have AGE inhibitors such as aminoguanidine and benfotiamine – all with limited success in neuropathy (Balakumar et al. 2010, Schemmel et al. 2010). However, the development of RAGE inhibitors remains an attractive therapeutic target.

Hypoxia

Given the microvascular damage associated with poorly controlled diabetes, it is unsurprising that this is a potential mechanism of neuropathic damage. Occlusion of the vasa nervorum (by the gradual accumulated extravasated AGEs described above) is associated with hypoxic damage to the endoneurium, leading to the neuropathy. This is along the same mechanism associated with the microvascular damage associated with diabetic retinopathy (Stevens et al. 1995).

Hyperlipidemia

The classic dyslipidemia of poorly controlled diabetes is the high levels of total cholesterol, high levels of LDL, low levels of high-density lipoprotein, and high levels of triglycerides. In addition to the high cardiovascular risk that these biochemical abnormalities confer, they are also significantly associated with the development of diabetic neuropathy (Vincent et al. 2011).

High free fatty acid levels are also associated with the development of neuropathy. High levels of free fatty acids are associated with a proinflammatory state, with increased levels of inflammatory cytokines, raising oxidative stress. Furthermore, the insulin-resistance and resultant hyperglycemia that characterizes type 2 diabetes is associated with intramuscular accumulations of free fatty acids – thus perpetuating the problems.

Although there are in vitro and animal data suggesting that dyslipidemia leads to accumulation of sorbitol and other intermediary metabolites, the exact mechanisms by which high lipid levels interfere with neuronal function remains to be elucidated.

AREAS OF CONTROVERSY AND/OR FUTURE RESEARCH

- Work continues to accurately identify the molecular causes of neuropathy – in particular painful neuropathy – and several drugs are in development that block the above described metabolic pathways and the accumulation of harmful molecules
- Understanding these metabolic pathways should allow the development of new agents to target appropriate receptors in an attempt to bring symptom relief to the millions of people around the world who continue to suffer as a result of this debilitating complication of diabetes
- An expanding research base is bringing together abnormalities in structure and function to determine the pathophysiology of diabetic neuropathy
- As the incidence and prevalence of diabetes continues unabated, especially in parts of the world where access to health care is limited, it is likely that there will be an increase in the number of people developing micro- and macrovascular complications, despite the awareness that good glycemic control and multiple risk factor management helps reduce the likelihood of them occurring
- The challenge for researchers and pharmaceutical companies is to make any new treatments developed accessible and affordable to those who are most at risk of developing these complications
- Until recently, due to the requirements of the regulatory authorities to develop new treatments compared with placebo, it has been difficult to determine which of the treatments is likely to be most beneficial
- Those treating patients with peripheral neuropathy are heartened to see some companies take the initiative and undertake comparative 'head-to-head' trials to help determine a realistic treatment algorithm
- With the advent of genomic medicine there is a hope that individualized treatments will become possible, to ensure that the most appropriate agents will be prescribed according to an individuals' genetic susceptibility

IMPORTANT FURTHER READING

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