Section 1

1.1. Search methods for identification of studies:

Electronic searches
We searched PubMed, CENTRAL (The Cochrane Library 2012), MEDLINE (1993 to till date), and EMBASE (1993 to till date) for RCTs, cohorts, case control and cross-sectional studies in English language only, using the following search terms: (loss of protective sensation, diabetic neuropathy or diabetic polyneuropathy or peripheral nervous system diseases, distal symmetrical polyneuropathy, painful neuropathy, diabetic foot) and (lifestyle interventions, insulin infusion or enhanced glycemic control, diet and exercise in diabetes). We also searched the Clinical Trials Registry of India (www.ctri.nic.in) for ongoing and recently completed trials.

Other resources
We reviewed books on diabetes and its management the bibliographies of the randomized trials and cohort studies and identified, contacted the authors and known experts in the field to help us in identifying articles on recent development and management of complications in diabetic peripheral neuropathy.
Section 2

Diabetes Mellitus

2.1. Definition

Diabetes mellitus is a clinical syndrome characterized by hyperglycemia caused by relative or absolute deficiency of insulin in the body. Hyperglycemia may have many causes but the most common ones are due to type 1 or type 2 diabetes (1).

Lack of insulin affects the metabolism of carbohydrate, protein and fat, and can cause significant disturbances of water and electrolyte homeostasis. Long standing metabolic derangement is associated with functional and structural changes in many organs, particularly those of the vascular system, which leads to clinical ‘complications’ of diabetes. These characteristics may affect eyes, kidneys and the nervous system (1).

Hyperglycemia is present as a single independent risk factor for disease of both small (micro vascular) and large blood vessels (macro vascular). Severe hyperglycemia if untreated may result in diabetic retinopathy. Less severe hyperglycemia or impaired glucose tolerance may be associated with atheroma formation in large blood vessels (1).

Etiological classification of diabetes mellitus

2.2. Type 1 diabetes

- Immune mediated: there is infiltration of the islets of Langerhans with mononuclear cells containing activated macrophages, lymphocytes, natural killer cells and B lymphocytes.
- β-Cell specificity of the destructive process, with the glucagon and other hormone-secreting cells remaining intact.

- Idiopathic

2.3. **Type 2 diabetes**

Type 2 diabetes is a more complex condition than type 1 diabetes because there is a combination of resistance to the action of insulin in liver and muscle together with impaired pancreatic β-Cell function leading to ‘relative’ insulin deficiency (1).

2.4. **Other specific types**

- Genetic defect of β-Cell function

- Genetic defect of insulin action (e.g. leprechaunism, lipodystrophies)

- Pancreatic disease (e.g. pancreatitis, pancreatectomy, neoplastic disease, cystic fibrosis, haemochromatosis, fibrocalculous pancreatopathy)

- Excess endogenous production of hormonal antagonists to insulin (e.g. growth hormone-acromegaly; glucocorticoids-Cushing’s syndrome; glucagon-glucagonoma)

- Drug induced (e.g. corticosteroids, thiazide diuretic, phenytoin)

- Viral infections (e.g. congenital rubella, mumps, Coxsackie virus B)

- Uncommon forms of immune mediated diabetes
• Associated with genetic syndromes (e.g. Down’s syndrome; Klinefelter syndrome; Turner’s syndrome) (1).

2.5. Gestational diabetes

The term ‘gestational diabetes’ refers to hyperglycemia occurring for the first time during pregnancy. Gestational diabetes is defined as the diabetes with first onset or recognition during pregnancy. During normal pregnancy, insulin sensitivity is reduced through the action of placental hormones and this affects glucose tolerance. The insulin-secreting cells of the pancreatic islets may be unable to meet this increased demand in women genetically predisposed to develop diabetes (1).
Section 3

Prevalence of Type 2 Diabetes Mellitus

3.1. Trends of type 2 diabetes worldwide

Population growth, ageing of populations, and urbanization with associated lifestyle changes is likely to lead to an increase of 50.7% worldwide by 2030. The largest increases are expected in the older age groups in low and lower-middle income countries with the age group of 60 years. Currently, the greatest number of people worldwide with diabetes is in the age group of 40-59 years, and this is predicted to remain so in 2030, to add on that there also will be a simultaneous increase in the age group of 60-79 years by 2030. The overall total percentage predicted increase in numbers with diabetes from 2011 to 2030 will be 50.7%, at an average annual growth of 2.7%, which is 1.7 times the annual growth of the total world adult population (2). Studies revealed that there is a marked increase in prevalence of diabetes worldwide, especially in developing countries as they adhere more to western lifestyle. Prevalence of risk factors like obesity in childhood has led to induction of type 2 diabetes in children and young adults.

Prospective population-based cohort studies suggest that the main pathophysiological defects leading to type 2 diabetes are insulin resistance and a relative insulin secretory defect. The main etiological risk factors for type 2 diabetes are age, obesity, family history, and physical inactivity. Dietary factors, such as a high proportion of energy consumed as saturated fat and low intake of fruit and vegetables, are likely to be important causative factors for developing type 2 diabetes (4).
A health survey conducted in United Kingdoms (UK) in 2006 estimated the prevalence of self-reported diabetes to be 5.6% in men and 4.2% in women. They found that there was a sharp increase in the prevalence of diabetes in UK with increasing age in both the sexes of the population. Though it is difficult to determine the true incidence of diabetes at a given point of time in the population, as they require repeated glucose tolerance testing which might be difficult to perform in densely populated countries of the world. It is found that a person having impaired glucose tolerance (126-200 milligram/deciliter (mg/dl)) testing is 10 times at the risk of developing diabetes than the person with normoglycemia (4).

A prospective study conducted from 1995-2006 in Alberta, Canada, reported increasing incidence and prevalence of diabetes among the population in urban and rural Alberta (5). From 1995-2006, the age- and sex-adjusted prevalence of diabetes increased 22% among people in urban residences compared to 35% increase for those in rural location. Another study conducted from 1995-2005 stated that the prevalence of diabetes in Ontario, Canada increased substantially during the past 10 years, and by 2005 already exceeded the global rate that was predicted for 2030 (6). They found during the study that diabetes prevalence increased by 69%, from 5.2% in a population of 79,08562 in 1995 to 8.8% of 76945 in 2005. Prevalence increased by 27% from 6.9% in a population of 84,57,720 in 2000 to 8.8% of 92,76,945 in 2005.

Researches in United States (U.S) have reported that diabetes has almost increased by approximately by 100% in past two decades and by 2050 it is expected to increase by 165% and the greatest increase is expected in an elderly population with 252% of women in the age group 65-74 and 537 % among men of age greater than 75 years (7). They further suggested that there is a dramatic increase in the incidence, prevalence and mortality due to diabetes in the elderly.
population, hence a constant surveillance of the situation is required with health policy that focus on improved quality of life among them (7).

In a study on the global estimate of the prevalence of diabetes for 2010 and 2030, Nita et al reported India to be the first country among the top 10 countries of the world where 87 million people are expected to get inflicted with diabetes by 2030. They will be mostly aged between 20-79 years (4). It clearly reveals the seriousness of the situation as it will also affect the younger population of the country. Though as reported by the authors, highest prevalence of diabetes (33.4 %) will be seen in Nauru by 2030.

3.2. Trends of type 2 diabetes in India

India is currently the second most populated country of the world. WHO estimated 60 % of the diabetic population will be from developing countries in Asia by 2025, that is the individuals with diabetes will increase from 240 million in 2007 to 380 million in 2025. In a survey done in 1995 by the World Health organization (WHO) it was estimated that there were 135 million diabetics in 1995, which is all set to increase to 300 million by 2025 (3).

Another estimate of the problem by Shaw et al in a study revealed that in 2010 there were 285 million people worldwide with diabetes, with considerable disparity between populations and regions. They further stated that most of the diabetics belonged to the developing countries with the age groups of 40-60 years at a higher risk of developing complications. The highest regional prevalence was reported for North America (10.2 %) followed by South Asia (6.7 %) (8).
A cross-sectional study on prevalence of diabetes, obesity and dyslipidemia in urban slum population in 2001 by Misra et al highlighted that there were high trends of prevalence of obesity, dyslipidemia and diabetes mellitus particularly in the middle age females (30). In a national survey in 2001 it was found that ratio of Impaired Glucose Tolerance (IGT) to diabetes was found to be greater than one, implying a greater chance of individuals with IGT to have diabetes in future (31). In another study by Ramachandran et al in 2003 on National Urban Diabetes (NUD) survey determining the prevalence of diabetes and IGT due to changing lifestyle in rural India, reported a three-fold increase in age and sex adjusted prevalence of diabetes (from 2.20% to 6.36%). They concluded from their study that disordered lifestyle, increased upper body adiposity and physical inactivity were the primary causes among Indians resulting in higher prevalence of diabetes and IGT in rural Tamilnadu, India (9).

Mohan et al did an epidemiological survey in urban parts of Chennai and found results that were surprising. During the survey they found that there had been an incredible increase in the prevalence of diabetes at an alarming rate. Prevalence of diabetes in Chennai was estimated to be 72% higher than that reported in 1989, and 6% higher than the NUD study (32), carried out just 3 years earlier. They also found that there appears to be a temporal shift, with the younger age groups being more affected. They found the prevalence of IGT to be lower, but that of diabetes increased in urban parts of Chennai. Two reasons were postulated for such trends observed in urban Chennai; firstly, increased conversion rates of IGT to diabetes could have been suggestive of slowing down of pace of the epidemic of diabetes in urban India, as the IGT (prediabetic) pool begins to shrink. Secondly, there could be a rapid progression from the normal state through IGT to diabetes, which could imply a rapid increase in the diabetes epidemic or a worsening diabetogenic environment. The authors further recommended performing prospective trials to
address the issue in Indian environment, so as to assess the exact changes occurring with regard to the diabetes epidemic in India (32).

It is well known that Asian Indians develop diabetes one or two decades earlier than Europeans (10). Hence we need to develop national policy on the management of diabetes and its related complications to address the issue. In an analysis of preventive measures by Narayan et al on global prevention and control of type 2 diabetes, they stated to include preventive measures in a clinical scenario for the management of type 2 diabetes and its complications. The authors further laid emphasis on early recognition of prediabetes and undetected diabetes for implementing effective measures on a single stage for the management of diabetes and its complications (33). Our focused national policies that are devised in the interest of diabetic population should have a cumulative effect at the national level to support people with diabetes and also provide them the armamentarium for the control of diabetes. Narayan et al further suggests for development of “cluster visits” with a multidisciplinary team of health care providers, for people with diabetes. Moreover, they had further emphasized that people with isolated prediabetes or diabetes can be referred for lifestyle interventions and follow-up. These focused policies will not only lead to risk reduction associated with diabetes and other non-communicable disease but will also bring down the prevalence of diabetes and its complications in India which set to rise to 69.9 million in 2025 (33).

3.3. Prevalence of diabetic peripheral neuropathy

The International Association for the Study of Pain (IASP) has defined neuropathic pain as “pain initiated or caused by a primary lesion or dysfunction in the nervous system” (14). Type 2 diabetes usually has two common complications either macrovascular or microvascular
Review of literature

complications. The most frequently occurring complication in type 2 diabetes is diabetic peripheral neuropathy (DPN) or distal symmetrical polyneuropathy (DSP). DPN affects up to 50% of the population with diabetes. Complications of DPN include severe pain, loss of ambulation and increased risk of foot ulceration and amputation (11).

Studies conducted in United States of America have reported that neuropathic pain syndromes have affected up to 70% of American population with diabetes (34). It is postulated that poor glycemic control and cardiovascular risk factors can contribute to the etiology of painful diabetic peripheral neuropathy. As such risk factors specific to painful neuropathy remains unclear (34). An observational study by Abbott et al in 2011 of a large cohort of diabetic patients receiving community-based health care in northwest England stated that painful symptoms had an occurrence of 26% in patients without neuropathy and an occurrence of 60% in patients with severe form of neuropathy in diabetes. Risk of painful neuropathic symptoms in type 2 diabetes was found to be double that of type 1 diabetes and it was noticed that symptoms were not affected by insulin use, foot deformities, smoking, or alcohol intake. Women had 50% increased risk of painful symptoms compared with men of same age. On comparison with South Asian population authors stated that South Asians without neuropathy maintained a risk of 50% for the development of painful neuropathy in diabetes (35).

In India though there haven’t been many trials to screen the current status for diabetic peripheral neuropathy, still one study has estimated an overall prevalence 19.1% for neuropathy in South Indian type 2 diabetic patients, age and duration of diabetes were identified risk factors for neuropathy (36). Diabetic peripheral neuropathy (DPN) is one of the commonest causes of foot complications like amputation and disability in ambulation. It accounts for frequent
hospitalization than other complications of diabetes and also is the most common cause of non-traumatic amputation (37). Another study conducted by Dixit et al on the awareness levels of type 2 diabetic patients in India found that there was a lack of awareness for diabetic foot care and further asserted the need to bridge the disparity in awareness regarding diabetic foot care among Indian masses with more aggressive preventive foot care strategies (38).

The Fremantle Diabetes Study was done in 2005 with the purpose to determine longitudinal predictors of impaired mobility and physical disability in patients with type 2 diabetes. After an average 4.6 ± 2.3 and 4.8 ± 2.3 years of follow-up in 818 and 934 patients, respectively, 28.5% of subjects had developed new mobility impairment and 18.1% had developed new ADL disability. Authors further stated that the risk of mobility impairment was significantly increased by older age (6%/year), peripheral neuropathy (40% increase), stroke history (123%), and insulin treatment (117%) (39). DPN is not only progressive in nature but is also associated with pain, loss of protective sensation leading to increased probability of falls in elderly thereby limiting their mobility and activity. Moreover it was found that due to decreased sensation at ankle in participants with DPN there was greater chance of postural instability, concluding that even during vision, postural control remains impaired in quite standing. This finding can be transmuted to the fact that in elderly with DPN there is a greater likelihood that they will encounter fall in their lifetime there by increasing the chance for morbidity and mortality. In a worldwide study on epidemiology of falls it was observed that women with diabetes have an increased risk of fall (39, 40). Cross-sectional data from the Third National Health and Nutrition Examination Survey, (US) indicates that among people with age 60 years and above, women with diabetes are 1.6 times more likely to have fallen in the previous year and twice as likely to have fall-related injuries than women without diabetes. Other prospective study reported that
older people with severe bunion, toe deformity, ulcer and deformed nails have a two-fold increased risk of falling when compared with the healthy counterparts. Approximately 10-20% of falls result in fractures, in which either they sustain fracture in the distal forearm or hip (41). Contributing to age-related frailty, restricted mobility and reduced quality of life.
Section 4

Functional Anatomy and Physiology

Usually blood glucose is tightly regulated within a narrow range in the body. A balance is maintained in the body once the glucose enters the body. A balance is preserved between the entry of glucose into the circulation from the liver, supplemented by intestinal absorption after meals, and glucose uptake by peripheral tissues, particularly skeletal muscle. A continuous supply of glucose is essential for the brain, which cannot oxidize free fatty acids and relies upon glucose as its principal metabolic fuel. After meals, usually the blood insulin levels rises. Insulin is an anabolic hormone with profound effects on the metabolism of carbohydrate, fat and protein (figure 1). Insulin is secreted from pancreatic β cells into the portal circulation, with a brisk increase in response to a rise in blood glucose. Insulin lowers blood glucose by suppressing hepatic glucose production and stimulating glucose uptake in skeletal muscle and fat, mediated by the glucose transporter, Glucose Transporter Type 4 (GLUT 4) (1).

Increased glucose transport occurs in the muscle cells either due to exercise (heavy-moderate) as exercising muscle becomes more permeable to glucose even in the absence of insulin or immediately after the meal, insulin is released in large amount by pancreas, it causes rapid transport of glucose into the muscle cells (42). Important functions of insulin are summarized in table 1.
Table 1: Metabolic actions of Insulin

<table>
<thead>
<tr>
<th>Anabolic effect (Increase)</th>
<th>Anti-catabolic effect (Decrease)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Carbohydrate metabolism</strong></td>
<td></td>
</tr>
<tr>
<td>Glucose transport (muscle, adipose tissue)</td>
<td>Gluconeogenesis</td>
</tr>
<tr>
<td>Glucose phosphorylation,</td>
<td>Glycogenolysis</td>
</tr>
<tr>
<td>Glycogenesis,</td>
<td></td>
</tr>
<tr>
<td>Glycolysis Pyruvate dehydrogenase activity,</td>
<td></td>
</tr>
<tr>
<td>Pentose phosphate shunt</td>
<td></td>
</tr>
<tr>
<td><strong>Lipid metabolism</strong></td>
<td></td>
</tr>
<tr>
<td>Triglyceride synthesis</td>
<td>Lipolysis</td>
</tr>
<tr>
<td>Fatty acid synthesis (liver)</td>
<td>Lipoprotein lipase (muscle)</td>
</tr>
<tr>
<td>Lipoprotein lipase activity (adipose tissue)</td>
<td>Ketogenesis</td>
</tr>
<tr>
<td></td>
<td>Fatty acid oxidation (liver)</td>
</tr>
<tr>
<td><strong>Protein metabolism</strong></td>
<td></td>
</tr>
<tr>
<td>Amino acid transport</td>
<td>Protein degradation</td>
</tr>
<tr>
<td>Protein synthesis</td>
<td></td>
</tr>
</tbody>
</table>
In response to a rise in blood glucose, e.g. after a meal, insulin is released, suppressing gluconeogenesis and promoting glycogen synthesis and storage. Insulin promotes the peripheral uptake of glucose, particularly in skeletal muscle, and encourages storage (as muscle glycogen). It also promotes protein synthesis and lipogenesis, and suppresses lipolysis. The release of intermediate metabolites, including amino acids (glutamine, alanine), 3-carbon intermediates in oxidation (lactate, pyruvate) and free fatty acids (FFAs), is controlled by insulin. In the absence of insulin, e.g. during fasting, these processes are reversed and favour gluconeogenesis in liver from glycogen, glycerol, amino acids and other 3-carbon precursors (1).

** (from Davidson’s Principle and Practice of Medicine 21st edition)
Section 5

Pathogenesis of Type 2 Diabetes

Diabetes mellitus is usually considered as a syndrome of impaired carbohydrate, fat and protein metabolism either caused by decreased sensitivity of the tissue to insulin or lack of insulin production by the body.

5.1. Type 1 diabetes

_Viral infections or autoimmune disorders_ may be involved in the destruction of β cells in many patients with type I diabetes, although heredity also plays a major role in determining the susceptibility of the β cells to destruction by these insults. Usually it affects children of age group of 14 years that is the reason why it is also called juvenile diabetes mellitus, but can occur in any age including adulthood. It may develop abruptly within a few days to a week; because of destruction of β cells of the pancreas it may lead to increased blood sugar, increased utilization of fat and protein in the body as the primary fuel, increased loss of protein in the body (42).

5.2. Type 2 diabetes

It is a far more common type of diabetes accounting for 90-95% of diabetes than type 1 diabetes. This type of diabetes is referred to as adult onset diabetes. Though in the recent years there had been a drastic increase with the prevalence of diabetes among the age group of 20 years and above, involving the younger age group in diabetes. This trend appears to be related mainly to the increasing prevalence of obesity, _the most important risk factor for type 2 diabetes_ in children and adults.
Obesity, insulin resistance and metabolic syndrome usually precedes before the development of type 2 diabetes (42).

5.3. Insulin resistance

Insulin resistance is defined as a condition of low insulin sensitivity in which ability of insulin to lower circulating glucose is impaired. Genetic predisposition combines with other factors like obesity, aging, elevated free fatty acids, and hyperglycemia which contributes to a pathological insulin resistant state.

Insulin resistance in muscle, adipose and liver tissue arises from multiple complex metabolic abnormalities. Biochemical defects that provoke insulin resistance usually involve impaired insulin signaling and reduction in glucose transport in the insulin resistant tissues (43).

5.4. Hepatic Insulin Resistance

The degree of abnormality in hepatic glucose output (HGO) positively and strongly correlates with degree of fasting hyperglycemia. This suggests that rate of HGO has a major role in contributing to fasting glucose levels. This implies that impaired levels of insulin and glucose are not able to regulate the suppression of HGO from the liver. In other words liver is insulin resistant and that is due to the decrease in the number of hepatic insulin receptors of the body. However elevated glucagon levels in the body can also contribute to reducing the suppressive effects of insulin and glucose on HGO (43).
5.5. Peripheral insulin resistance

Subjects with type 2 diabetes exhibit peripheral resistance in target tissues such as skeletal muscles. In the muscles, the defects in action are 1) impaired insulin receptor tryokinase activity, 2) diminished glucose transporters and 3) diminished glycogen synthatase and pyruvate dehydrogenase. These disturbances results in impaired intracellular pathways for glucose disposals, namely, glycogen synthesis and glucose oxidation (44).

Table 2: Development of Insulin resistance

<table>
<thead>
<tr>
<th>Phase</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>First phase</strong></td>
<td>Plasma glucose remains normal despite demonstrable insulin resistance because the insulin levels are increased.</td>
</tr>
<tr>
<td><strong>Second phase</strong></td>
<td>Insulin resistance tends to worsen which leads to post prandial hyperglycemia, despite elevated levels of insulin concentration.</td>
</tr>
<tr>
<td><strong>Third phase</strong></td>
<td>Insulin resistance does not change but decline in insulin secretion is observed leading to fasting hyperglycemia</td>
</tr>
</tbody>
</table>
Section 6

Diabetic Neuropathy

Diabetic neuropathy is heterogeneous in its presentation. It is associated with significant morbidity and is one of the most common complications of diabetes mellitus (44).

6.1. Etiopathogenesis

Hyperglycemia plays an important role in the pathogenesis of diabetic neuropathy. Other metabolic consequences like increased polyol pathway activity, myo-inositol depletion and Na+/K+ - ATPase activity (Sodium-potassium adenosine triphosphatase) also contributes to the pathogenesis of diabetic neuropathies.

I. Metabolic theory

a. Polyl pathway: In the presence of excess hyperglycemia, there is an intracellular accumulation of glucose. This excess glucose gets converted into sugar alcohol i.e. sorbitol by enzyme aldose reductase. Sorbitol accumulation has deleterious effect on nerve conduction velocity. This is attributed to Schwann cell damage caused by increase in osmolarity due to sorbitol and fructose (43, 44).

b. Myo-inositol metabolism: Myo-inositol is an important constituent of phospholipids and cell membranes. It is found in higher concentration in peripheral nerves. Hyperglycemia causes increased intracellular concentrations of glucose, resulting in increased activity of polyol pathway leading to depletion of myo-inositol concentrations that inhibits Na+/K+ ATPase tissue activity. Reduced
activity of Na+/K+ ATPase activity results in diminished myo-inositol uptake in the nerve (43).

c. Protein kinase C pathway activation (PKC): Hyperglycemia increases the formation of diacylglycerol, which in turns activates PKC. In addition hyperglycemia activates polyol pathway which causes depletion of myoinositol. PKC mediates a vascular response to hyperglycemia that involves both endothelium and smooth muscles. PKC regulates the vascular permeability, contractility, basement membrane synthesis and cellular proliferation. Inhibition of PKC due to euglycemia plays a pivotal role in decrease of vascular permeability and deregulation of basement membrane synthesis of the endothelium (43).

d. Advanced glycation end products (AGE): non-enzymatic addition of glucose to proteins is called glycation. Glucose forms a chemically reversible product with protein called as Schiff base. The degree to which glycation occurs depends on blood plasma glucose concentration (43).

e. Hexosamine pathway: is activated when excess intermediates are formed from increased glycolytic activity. These intermediates alter gene function and protein expression that contribute to diabetic microvascular complications (44).

II. Vascular theory

The normal ‘vascular auto regulation’ seems to be lost. The hypoxia that occurs due to decreased blood flow leads to endoneural hypoxia and thereby decreasing Na+/K+ ATPase. This
reduces nerve conduction velocity by decreasing axonal transport and leads onto axonal atrophy. The diabetic nerve demonstrating multifocal loss of proximal fibers and diffuse loss of distal fibers are usually vascular in origin (44).

Usually it is observed that in diabetic individuals there is a proliferation of endothelial cells of the endoneural vessels due to increase in thickness of the basement membrane there is closure of the lumen of the vessels (figure 2).

Figure 2: Normal and damaged nerves
6.2. Definition, Stages and classification of Diabetic Neuropathy:

**Definition**

American Diabetes Association (ADA) published a statement on diabetic neuropathies as “the presence of symptoms, and/or signs of peripheral nerve dysfunction in people with diabetes after exclusion of other causes”.

Confirmed clinical neuropathy is defined as clinical neuropathy plus confirmation by abnormal quantitative neurological function tests (e.g. electrophysiological test, quantitative sensory testing or autonomic function tests). Whereas, subclinical neuropathy is defined as presence of an abnormal quantitative sensory neurological testing with little or no evidence of clinical neuropathy on examination (45).

6.3. Stages in Diabetic Neuropathy

**Table 3: Stages as defined by the criteria given by the Mayo clinic**

<table>
<thead>
<tr>
<th>Stage</th>
<th>Description</th>
<th>Signs or Symptoms</th>
<th>Abnormal Quantitative sensory tests</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
<td>No neuropathy</td>
<td>No</td>
<td>No</td>
</tr>
<tr>
<td>1</td>
<td>Subclinical neuropathy</td>
<td>No</td>
<td>Yes</td>
</tr>
<tr>
<td>2</td>
<td>Clinically evident neuropathy</td>
<td>Yes</td>
<td>Yes</td>
</tr>
<tr>
<td>3</td>
<td>Debilitating neuropathy</td>
<td>Yes</td>
<td>Yes</td>
</tr>
</tbody>
</table>
6.4. Classification of diabetic peripheral neuropathy

A symmetrical distal neuropathy is the most common presentation of diabetic neuropathy. It can be symptomatic in patients complaining of numbness, tingling, and burning in the feet and lower shins or it can be asymptomatic, first detected on neurological examination or electrophysiological testing (46).

Classification of diabetic neuropathy

I. Symmetrical distal neuropathy

II. Symmetrical proximal neuropathy

III. Asymmetrical proximal neuropathy
   a. Cranial
   b. Trunk radiculopathy or mononeuropathy
   c. Limb plexus or mononeuropathy
   d. Multiple mononeuropathy
   e. Entrapment neuropathy
   f. Ischemic nerve injury from acute arterial occlusion

IV. Asymmetrical neuropathy and symmetrical distal neuropathy
6.5. Types of diabetic neuropathy

I. Focal neuropathies

   a. Ischemic neuropathies

      1. Sudden onset

      2. Asymmetrical

      3. Ischemic etiology

      4. Self-limited

   b. Entrapment neuropathies

      1. Gradual onset

      2. Usually asymmetrical but can be bilateral

      3. Compression etiology

      4. Waxing and waning progressive course without spontaneous recovery

II. Diffuse neuropathies

   a) Insidious onset

   b) Symmetrical

   c) Abnormalities secondary to vascular, metabolic, structural and autoimmune aberrations
d) Progressive without spontaneous recovery
Section 7

Documentation of Neuropathy

7.1. Clinical Presentation

Symptoms of DPN may vary from patients to patients, but common complaints are numbness, tingling and pain beginning in the toes and soles of the feet, ankles and lower shins. Patients often enlist another description of pain as dead feeling in the feet, burning sensation in the feet, pins and needles in the feet (table 4) (Paresthesia). In addition to this, other types of pain also get superimposed for example shock like, electric or icepick pain which frequently complicates the lives of patients with diabetic neuropathy. Other descriptors used by patients include jabbing, throbbing, icy cold, cramping, intense itching. Sensory symptoms are usually worse at night when the patient is trying to sleep. Often, patients with diabetic neuropathy states that movement, walking or standing lessens the pain. Balance problem is also increasingly common among people with neuropathy, usually dynamic or static balance is affected in diabetic peripheral neuropathy (45).

7.2. Types of pain

Dysesthetic pain is associated with increased firing of cutaneous and subcutaneous distribution of damaged nociceptive fibers, particularly sprouting regenerating fibers. Paraesthetic pain is thought to occur from various possible etiologies: (1) spontaneous activity and increased mechanosenstivity near the cell body of damaged afferent axons in the dorsal root ganglion; (2) loss of segmental inhibition of large myelinated fibers on small unmyelinated fibers (3) ectopic impulses generated from demyelination patches of myelinated axons
The third type of pain is muscular pain. These are ectopic neural impulses to the muscles that might be generated from the demyelinating patches in motor nerves. Muscular pain descriptors includes “dull-ache”, “night cramps”, “band like sensation”, “drawing sensation”, “toothache-like”. Treatment for muscular pain includes lower limb stretching exercises twice a day and proper footwear’s including metatarsals bars if required. If muscle pain continues after 2 weeks of exercise usually a muscle relaxant should be considered (45).

Table 4: Descriptors of different kinds of neuropathic pain

<table>
<thead>
<tr>
<th>Dysesthesia</th>
<th>Paresthesia</th>
<th>Muscular pain</th>
</tr>
</thead>
<tbody>
<tr>
<td>• Burning sensation</td>
<td>• Pins and needles</td>
<td>• Dull ache</td>
</tr>
<tr>
<td>• Skin tingles</td>
<td>• Electric like</td>
<td>• Night cramps</td>
</tr>
<tr>
<td>• Painful sensation when bed sheet and stockings touches me</td>
<td>• Numb but achy</td>
<td>• Band like sensation</td>
</tr>
<tr>
<td></td>
<td>• Knife like shooting</td>
<td>• Deep aches, spasms</td>
</tr>
<tr>
<td></td>
<td>• Pain, lancinating pain</td>
<td></td>
</tr>
</tbody>
</table>

7.3. Motor signs and symptoms

Imbalance of walking is a commonly elicited complaint even if not volunteered by the patient initially. Patients may have gait ataxia while walking in the dark yet no ataxia during the day. This relates to loss of joint position sense of feet. Leg weakness is usually a late feature of
diabetic neuropathy, as patients usually do not complain of toe weakness, the first body region to be affected by weakness in most people with diabetic neuropathy.

7.4. Symptoms of autonomic neuropathy

Autonomic neuropathy in diabetes affects many organ systems, including the skin, the conduction system of the heart, gastric bowel motility, urinary bladder, and sexual functions. Patients complain of a range of symptoms from dry, cracked and mottled skin, dizziness, syncope and abdominal bloating after eating, diarrhea or constipation, urinary retention or incontinence and penile erection and ejaculation impairment. It is well known that resting tachycardia and silent myocardial infarction is common in diabetic patients (45).

7.5. Neurologic examination

The physical examination begins with vital signs and need for checking the pulse and blood pressure measurements in several positions (supine, sitting and standing) to assess pulse and orthostatic change. Patients with symptoms that are suggestive of orthostatic hypotension should be clinically evaluated and all clinical measurements should be delayed for 1 minute after the change in position. Patients with normal cardiac function should have a rise of pulse of 20 to 30 when they changes position. Patients having dry, cracked skin, changes in nails and skin discoloration may have underlying autonomic neuropathy (45).

In mild diabetic distal neuropathy, the two most prominent changes on neurological examination will be reduced or lost ankle reflexes and a distal gradient loss of large and small sensory fiber modalities or “stocking and gloves” sensory loss. Examination of vibration senses using 128 Hz tuning fork is the most practical way to check the presence or absence of vibratory
senses at the feet. Over time the deficit may move proximally to the metatarsal-phalangeal joints, dorsum of the foot, ankle and mid-shin or knee (45).

7.6. Monofilament testing

Performing monofilament testing on the plantar surface of great toe and pulp of the index finger bilaterally can assess sense of touch. The current available device is known as Semmes-Weinstein monofilaments (SWM). They are usually made of fine nylon and are designed in a way that the amount of pressure on the plantar surface is the function of instrument not the examiner. They are calibrated, single-fiber nylon threads, identified by values ranging from 1.65 to 6.65, that generate a reproducible buckling stress. The higher the value of the monofilament, the stiffer and more difficult it is to bend. In common clinical practice usually three monofilaments are used to diagnose peripheral neuropathy they are 4.17, 5.07 and 6.10 (47). Each monofilament is marked with a number that represents the decimal log of 10 times the force in milligrams ranging from 1.65 (000.45 gm (gram)) to 6.65 (447 gm) of linear force (47).

In examining the feet, a series of monofilaments that range in sizes from 2.83 to 6.65 are typically used. The tip of the monofilament is gently placed perpendicularly on the surface until the monofilament buckles. The approach, the skin contact and the departure of the monofilament should be 1.5 seconds approximately (45). Examiner should not allow the monofilament to slide or make contact with the skin again. Lists of monofilament with their target force and evaluator size are enlisted in table 5.

Sensitivity of monofilament ranges from 0.41 to 0.93 and specificity varies from 0.68 to 1. Though this difference usually seems to be because of variability in the number of sites being
tested (47). The examiner should also be sure to avoid callus area. Patients without neuropathy should be able to sense 3.61 monofilament (equivalent to 0.4 gm of linear force). The inability to sense 4.17 (equivalent to 1 gm of linear force) or higher is considered consistent with neuropathy. Inability to sense 5.07 is consistent with loss of protective sensation.

Figure 3: The minimum number of sites suggested by American College of Physicians for assessment of neuropathy using 10 gm monofilament (This content has been excerpted from the ACP Clinical Skills Module, "Diabetic Foot Ulcers.")

A prospective multicenter trial done by Pham et al. on 248 patients found that foot ulcers developed in 95 feet (19%) or 73 patients (29%) during the study. Patients who developed foot ulcers were more frequently men, had diabetes for a longer duration, had a high Neuropathy Diabetes Score (NDS), had a high vibration perception threshold (VPT), and had an inability to feel a 5.07 SWM. They stated that combination of the NDS and the inability to feel a 5.07 SWM reached a sensitivity of 99% (48).
Table 5: Monofilament table

<table>
<thead>
<tr>
<th>Evaluator size</th>
<th>Target force in grams</th>
<th>Plantar threshold</th>
</tr>
</thead>
<tbody>
<tr>
<td>1.65</td>
<td>0.008</td>
<td></td>
</tr>
<tr>
<td>2.83*</td>
<td>0.007</td>
<td>Normal</td>
</tr>
<tr>
<td>3.61*</td>
<td>0.4</td>
<td></td>
</tr>
<tr>
<td>3.84</td>
<td>0.6</td>
<td></td>
</tr>
<tr>
<td>4.08</td>
<td>1</td>
<td>Diminished light touch</td>
</tr>
<tr>
<td>4.17</td>
<td>1.4</td>
<td></td>
</tr>
<tr>
<td>4.31*</td>
<td>2</td>
<td></td>
</tr>
<tr>
<td>4.56*</td>
<td>4</td>
<td></td>
</tr>
<tr>
<td>4.74</td>
<td>6</td>
<td>Diminished protective sensation</td>
</tr>
<tr>
<td>4.93</td>
<td>8</td>
<td></td>
</tr>
<tr>
<td>5.07*</td>
<td>10</td>
<td>Loss of protective sensation</td>
</tr>
<tr>
<td>6.65*</td>
<td>300</td>
<td>Deep pressure sensation only</td>
</tr>
</tbody>
</table>
In the table, the most important calibrations are: 3.61, 4.31, 4.56, 5.07 and 6.65 are marked (*).

The patients unable to sense 3.61 size are presumed not to have small fiber neuropathy. Patients, who are able to sense 5.07 monofilament, have retained protective sensation even if they have mild small fiber neuropathy. Inability to sense the 5.07 monofilament (10 gram) is consistent with severe neuropathy greatly increases the chances of neuropathic ulcers.

7.7. Deep tendon reflexes

Documentation of ankle and knee reflexes is an important part of physical examination in patients with known or suspected peripheral neuropathy. Deep tendon or muscle stretch reflexes are absent in a length dependent pattern such that the ankle reflexes are typically lost first followed by knee reflexes. Upper limb reflexes are usually preserved in early diabetic yet as the disease progresses they either become reduced or absent. In neuropathy as the duration of diabetes increases to 15-20 years it is common for the arms and legs to become areflexic (45).

7.8. Motor Function

Loss of motor function most commonly follows the changes in sensation and reflexes.

Many patients will have no demonstrable weakness in lower limbs on strength testing even after years of diabetic neuropathy.

Typically weakness will be first detected in the toe extensors followed by the toe flexors, a pattern that follows the length dependent nature of diabetic neuropathy. As the disease progresses patients develop weakness of dorsiflexors and eversion before ankle plantar flexion and inversion. Proximal muscles of the legs are often spared unless the diabetic neuropathy is unusually long-standing approximately 25-30 years (45).
Once diabetic neuropathy advances to the level of the knee, patients begin to complain of hand weakness and the examination often confirms the deficits. Usually weakness will start in the lower limbs in dorsal and ventral interossei muscles and abductor digiti minimi.

### 7.9. Electrophysiological testing

Electrophysiological testing plays a major role in evaluation of patients with distal symmetrical polyneuropathy using motor and sensory nerve conduction studies. Though the neuropathies associated with diabetes mellitus represents insidious and progressive processes for which a disconnection exists between pathological severity and the development of symptoms (49).

DPN is a major cause that initiates the pathophysiological pathway to foot ulceration and amputation, and from a public health perspective, leads to extensive deterioration of quality of life and economic burdens (50). Electrophysiological testing not only defines the fibers that are affected in DPN (motor and sensory), but also renders a gross estimate of the duration of the neuropathy, and even gives an insight into the prognosis (51).

Nerve conduction studies measure the ability of peripheral nerves to conduct electrical signals and are abnormal when pathological changes are present in the myelin, nodes of ranvier, and axons (49). Routine nerve conduction studies include evaluation of motor function of the median, ulnar, peroneal, and tibial nerves, and sensory function of median, ulnar, radial, and sural nerves. Standard unit for velocity is in meter per second, motor amplitude is in millivolts, and sensory amplitude is in microvolts. These measurements of upper and lower limb motor and
sensory nerve studies show the presence, distribution, and severity of peripheral nerve disease in type 2 diabetes (51).

Nerve conduction studies have always been considered the gold standard for the diagnosis of neuropathy. Nerve conduction studies (NCS) correlate with clinical scores, nerve amplitude reflects the degree of nerve fiber loss. NCS reduces variance among testing and appears to be the most efficacious and reliable source of investigation in DPN. Usually NCS abnormalities are detected in 45%-60% of patients with type 2 diabetes. Severity of abnormality in NCS reflects a correlation with the glycemic levels and usually abnormal NCS increases with the duration of diabetes (49). A study by Resnick et al., demonstrated reductions in walking speed, static balance, dynamic balance, and coordination in a population of aged people with diabetes as compared to those without diabetes on abnormal electrophysiological test in neuropathy (52).

It is true that in most of the neuropathies usually sensory nerves gets affected more than motor nerves. In severe cases, action potentials cannot be recorded in lower limb. Hence in such conditions the rule of thumb is to check the suspected nerves of upper limb. The amplitude of motor compound muscle action potentials and sensory nerve action potential can be used to estimate the number of intact motor and sensory nerve fibers respectively, unless a demyelinating process is present between the point of stimulation and recording electrodes. Though nerve conduction studies measures the dysfunction in large diameter fibers hence it might be possible in a patient with small fiber dysfunction to have normal NCS despite of complains of pain in patients (49).
In a 6 years follow-up of diabetic patients it was found that MNCV is an independent predictor for the development of new foot ulcers in people with diabetes (43, 96). Clinical studies have used MNCV as a “benchmark” for the assessment of distal symmetrical diabetic polyneuropathy, as it is a very reproducible and objective method of assessment (23, 53 and 54). Other methods can be used to measure DPN which include the assessment of sensory modalities using vibration threshold.

**Common Peroneal nerve conduction**: a clinical neurophysiological study of common peroneal neuropathy comprising of 103 patients revealed that the neuropathy was bilaterally present in 13 patients. Neurophysiological study suggested that axonal involvement was present in 64 patients, and conduction blocks were seen in 23 patients. The most frequently occurring lesion was axonal degeneration regardless of etiology of common peroneal neuropathy. The peroneal motor nerve conduction study recording from tibialis anterior was reported to be the single most important electrophysiological finding (23).

The reported values for common peroneal nerve conduction velocity of below knee segment is 48.3± 3.9 m/s (meter/second) and that of above knee segment is 52±6.2 m/s. The latency at ankle stimulation is 3.77±0.86 ms (milliseconds) and distal compound muscle action potential (CMAP) is 5.1±2.3 mV (millivolts) (54). The reported values of Indian population for NCS below knee segment is 46.54 ± 4.4 m/s and that across the fibular neck is 49.67±8.77 m/s. The latency at the ankle is 4.55 ± 0.59 ms and the distal CMAP amplitude is 4.23±1.61 mV (55).

**Tibial nerve conduction**: damage to the tibial nerve in the popliteal fossa is uncommon, however in diabetic peripheral neuropathy tibial nerve frequently gets affected in conjunction with peroneal nerve. Tibial neuropathy may result in the weakness of plantar flexors, invertors,
and the intrinsic foot muscles. For tibial nerve conduction study, the active surface recording electrode was placed on abductor hallucis, slightly below and anterior to navicular tuberosity. Surface stimulation was given behind and proximal to the medial malleolus and in the popliteal fossa. The normal conduction velocity of tibial nerve in Indian population is 48.3±4.5 m/s (55).

**Sural nerve conduction:** compression injury to sural nerve can occur due to baker cyst, resting leg against hard objects. It is often involved distally in diabetic peripheral neuropathy. Nerve conduction velocity might get slowed down in metabolic neuropathy. The surface electrodes are kept between the lateral malleolus and tendoachilles junction that records nerve conduction of the sural nerve. The nerve is stimulated antidromically 10-16 cm proximal to the recording electrodes, distal to the lower border of gastrocnemius at the junction of middle and lower third of leg. Sural nerve conduction velocity among healthy Indians was found to be approximately 50.9±5.4 m/s with an amplitude (Sural Nerve Action Potential (SNAP)) of 18±10.5 µV (55).

**7.10. Quantitative sensory testing**

Quantitative sensory testing (QST) is an essential method for quantifying sensory function in patients with polyneuropathies and specifically in DPN. The different modalities of QST have measurement errors as high as, or higher than the 30% associated with amplitude measures in NCS (56). Though precision can reduce the error significantly if standardized methods of assessments are used, but still it cannot achieve the precision of motor and sensory conduction velocity measures of NCS (49). The precision of QST devices are quite variable, as are the correlations with NCS. Vibration perception threshold (VPT) can be obtained with a simple, relatively inexpensive device, which is comparable to those obtained using more elaborate equipment and testing methods. Commonly assessment of tactile functions include
measurement of light pressure and vibration which usually evaluates large fiber and dorsal column function, whereas thermal and pain detection can be used to assess the integrity of small fibers and spinothalamic tract function (56). Vibration perception threshold determined through neurothesiometer is more reflective of peripheral nerve functions (57). Thermal threshold testing is generally considered to be less reliable than VPT testing, which reflects the complexity in the objective measurement of small fiber function. Variances of 50% and higher in thermal thresholds limits the diagnostic value and the utility of this end point in clinical trials (58).

The major limitation of QST is the psychophysical nature of the examination, since the test relies on subjective responses from the patient (59). Unlike NCS a practical limitation observed in QST is the absence of any standardized procedures which can translate VPT observations into a more clinically relevant outcome. Usually the findings with VPT measurements are reported with ‘volts’ as the unit, some researchers have used ‘micron’ of detectable displacement. Usually values from 20-25 volts are described as impaired vibratory perception, values equal to or greater than 25 as a presence of neuropathy and the values above 30 volts are identified as the presence of severe neuropathy (59).

7.11. Clinical scoring scales

Usually clinical scores are developed to provide wider information regarding the neurological assessment in diabetic neuropathy. Many scales are developed for clinical assessment and grading of severity in DPN. Neuropathy impairment scales were developed over time for assessment of diabetic neuropathy which includes NCS, vibration perception thresholds (VPT) and autonomic functions (heart rate with deep breathing) in percentile of the abnormalities reported which was then converted to a point system. Drawbacks of such scales
are that its time consuming, overtly detailed and very difficult to inculcate in day to day practice in a clinical scenario. Additionally, the point assignment on the Neuropathy Impairment Score (NIS) Lower Leg (LL) + 7 scales is heavily weighted by motor findings [64 of a maximum of 88 points for the NIS (LL)] (45).

In an effort to devise a scoring system that is feasible in a clinical scenario Michigan Neuropathy screening instrument was developed. This instrument includes a 15-item questionnaire and a simple clinical examination of the feet. The subjective assessment includes 15 ‘yes’ and ‘no’ type questions. Responses are then added to obtain the total score. Responses of “yes” to questions 1-3, 5-6, 8-9, 11-12, 14-15 are each counted as one point. A “no” response on question 7 and 13 are counted as 1 point. Question number 4 is a measure of impaired circulation and question number 10 is a measure of general asthenia and is not included in scoring.

The questionnaire is followed by a brief clinical examination involving 1) foot inspection for deformities, dry skin, callus, infection, or ulceration, 2) assessment of vibration sensation at the dorsum of the great toe (normal, reduced, or absent), and 3) grading of ankle reflexes (normal, reduced, or absent). Foot deformities include hammer toe, overlapping toe, hallux valgus, joint subluxation, prominent metatarsal head, and medial convexity (Charcot foot). Abnormality is determined by the number of positive responses or abnormal clinical findings. In both the subjective and objective portion of the MNSI, greater the score, greater is the neuropathy associated changes with diabetes.

Michigan diabetic neuropathy score (MDNS) is a 46 point clinical score was developed by Feldman et al. The MDNS consists of two parts, each of which is easily conducted in routine
clinical practice: a clinical neurological examination followed by routine nerve conduction measurements (60).

In MDNS Vibratory threshold perception, pain, and light touch are assessed with a 128 Hz tuning fork, a pin, and a 10 gm filament, respectively. As evidences suggests mono filaments, as a measure of touch perception, can indicate the pressure threshold that confers protection against plantar ulceration (48). The 10 gm filament is applied to the dorsum of the great toe, and the patient is asked to respond "yes" if he or she feels the filament. Eight correct responses out of 10 applications is considered normal (score of 0); 1-7 correct responses indicates reduced sensation (score of 1); and no correct answers translate into absent sensation (score of 2). Tendon reflexes are scored as 0 for normal, 1 for abnormal, and 2 for absent responses. Muscle strength is scored as 0 for normal, 1 for mild to moderate, and 2 for severe weakness, while complete loss of strength is scored as 3. Absent reflexes, absent sensation, and severe weakness are scored as 2. Nerve conductions (sural, peroneal motor, median sensory and motor, and ulnar sensory) are graded separately: 0 for normal and 1 for abnormal values (60).

Cross-sectional study by Feldman et al for early diagnosis of distal polyneuropathy had compared two clinical scores MNSI and MDNS and found MNSI to be a good screening instrument and MDNS coupled with NCS provides an easy way to confirm the diagnosis (60).

7.12. Clinical utility of Posturography

Despite of various clinical tools available in practice to assess balance issues in various conditions, still there remains a disparity to the naked eyes to differentiate between causes (i.e. specific abnormalities in postural control) and effects (i.e. the consequential imbalance) (61).
The current management of patients with postural instability is hampered by the intricate assessment of balance disorders. The current standard in clinical practice is a combination of history taking and physical examination, but neither approach is infallible.

Postural stability is usually defined as the ability to modify postural strategies in response to changing surface and environmental demands. This response is impaired in diabetic peripheral neuropathy leading to higher risks of fall (62). The only study that evaluated individuals with diabetes on deformable surfaces (foam) was by Lord et al in which the authors had excluded participants with diabetic peripheral neuropathy. Moreover, their degree of postural stability measures were evaluated using a simple sway meter attached at the level of waist (56), which might have caused varied results as compared to pragmatic standards of evaluation established by posturography for examination of balance impairments in population with DPN. They also reported that participants with diabetes had a greater sway amplitude as compared to healthy controls. The authors postulated diabetes to be the sole cause for balance impairments. However, Lord et al evaluated participants with diabetes on different surfaces (foam and normal surfaces), but the study had some major flaws, the sample size of the study was small to conclude that diabetes can be a sole cause of balance impairments. In addition, individuals with neuropathy were not evaluated to confirm this hypothesis (63).

Another study by Ahmed et al intended to compare the degree of asymmetrical weight distribution of the limbs, Anteroposterior (AP), and Mediolateral (ML) displacements by evaluating three groups of population that is participants with DPN, participants with diabetes only and healthy age matched controls. They concluded that participants with DPN had a far greater postural sway as compared to participants with diabetes mellitus and healthy controls.
(64). This study again had a small sample size. To add further to the current evidence a study by Lafond et al reported that even with vision ankle strategies were impaired in quiet static stance in DPN (65). They included 11 DPN elderly participants and found that ankle motor activity is affected in DPN during quiet standing emphasizing on postural instability in ML direction in DPN (65). Helene et al in a study found that COP-COM variable displacement were significantly larger in AP and ML direction for the DPN population as compared to healthy controls (40).

In conclusion there are various data on postural instability suggests that due to diabetes and its complications postural strategies are compromised on even or uneven surfaces. There appears to be a need for a well-designed trial using posturography as an outcome measure to address the issue of balance impairments in the diabetic population.

7.13. Quality of life in diabetic peripheral neuropathy

WHO defines Quality of Life as “individual’s perception of their position in life in the context of the culture and value systems in which they live and in relation to their goals, expectations, standards and concerns” (66). Studies have stated a correlation between the mortality rate and health related quality of life in type 2 diabetes. Quality of life as reported by patients are the patient’s perspective on health, disease, which is easily missed in a clinical scenario. In type 2 diabetes a comprehensive assessment which includes health related quality of life (HQOL) and health assessment should be undertaken rather than just emphasizing on strict glycemic control regimes. A study done by Kleefstra et al found that health related quality of life is an independent marker of mortality and further suggested to look beyond clinical parameters in type 2 diabetes (67). Another study by Landman et al on health related quality of life and mortality in general and elderly population with type 2 diabetes revealed that lower physical and
mental HRQOL was associated with higher rates of total mortality and cardiovascular mortality in type 2 diabetes (68).

There is a shift in paradigm of diabetes and its complications, population with diabetes world-wide are prone for early complications in diabetes leading to a poor quality of life and increased mortality. DPN is the single leading cause for amputations in diabetes. It also causes small fiber neuropathy which is associated with pain, disrupted sleep and may be a cause for depression leading to a reduced quality of life in diabetes. Usually there is a poor quality of life reported in patients with diabetic foot ulcers on comparison with general population and patients with diabetes (69). A study done by Nabuurs-Franssen et al in 2005 revealed that patients with healed ulcers had a better quality of life than patients with persisting ulcers. Moreover it also appears to be an emotional burden on the patient’s caregiver, hence revealing the seriousness of the situation in DPN (70). Vileikyte et al designed a scale specific to the neuropathy population in diabetes with an objective to measure patient’s perception and impact of diabetic peripheral neuropathy on quality of life and to measure the psychometric properties of the instrument in a population of patients with varying severity and symptomatology. They found three physical symptom measures and two psychosocial functioning measures with good reliability (alpha = 0.86-0.95). NQOL was more strongly associated with measures of neuropathic severity than SF-12; they found NQOL addresses the key dimensions of the patients' experience of diabetic peripheral neuropathy and is a valid tool for studying the impact of neuropathy and foot ulceration on quality of life (40).

At present there is a need for trial addressing the current situation of DPN in India, where the quality of life of patients with DPN needs to be evaluated. Moreover, India is the second
most populated country of the world which is set to have a boom in prevalence and incidence of diabetes related complications by 2030.
Section 8

Non pharmacological management of type 2 diabetes and diabetic neuropathy

8.1. Aerobic exercise in type 2 diabetes mellitus

Population growth, ageing of populations, and urbanization with associated lifestyle changes is likely to lead to an increase of 50.7% worldwide by 2030 (2). Another estimate of global diabetes prevalence and most recent projections for the future indicates that diabetes now affects 246 million people worldwide and is expected to affect some 380 million by 2025, representing as much as 7.1% of the global adult population (71). Prevalence of type 2 diabetes progressively affects middle aged and younger population worldwide. The changing lifestyle, physical inactivity and dietary habits clearly signifies that there is a shift in global epidemiology for type 2 diabetes, and its complications like neuropathy, retinopathy and nephropathy, myocardial infarction and stroke or mortality are on verge to rise in Indian population.

In accordance with lifestyle intervention programs consisting of regular exercise with or without dietary modulation and/or oral blood glucose-lowering medication have proven an effective therapeutic strategy in type 2 diabetes. A current guideline from American Diabetes association (ADA) and American college of Physicians (ACP) recognizes the strength of exercise in modulating diabetes and preventing it from further progressing to its macrovascular or microvascular complications (71). The ADA states that “to improve glycemic control, assist with weight maintenance, and reduce risk of cardiovascular disease, at least 150 min/week of moderate intensity aerobic physical activity is recommended and/or atleast 90 min/week of
vigorous aerobic exercise distributed over at least 3 days/week and with no more than 2 consecutive days without physical activity” (18).

8.2. Beneficial effects of exercise in type 2 diabetes mellitus

Daily exercise of 135 to 270 minutes per week for 2-6 months duration, have multiple benefits like glycemic control, changes in body composition, modulation of risk factors, vascular affects and improved myocardial function (19).

8.3. Glycemic control

Studies have stated modest effect of endurance training on metabolic control (increased insulin sensitivity, HbA1c, blood glucose control). Usually exercises of moderate intensity of 50-70 % of VO2 max have proved to have beneficial effect in type 2 diabetes. In addition, previous researches have shown improved insulin sensitivity and reductions in hyperglycemia related medications as a result of exercise training (19). In a meta-analysis by Normand et al, exercise training reduces HbA1c (0.66 %), that’s a significant reduction to prevent any diabetic complications (25).

8.4. Body composition

Endurance exercise training has yielded modest effect on body composition, subcutaneous fat and visceral fat. Though body composition can be altered surgically, still the visceral adiposity cannot be modulated by surgical means. On the other hand, endurance exercise has a positive beneficial effect on visceral fat. Weight loss relates to energy expenditure; aerobic exercise training has a greater potential to yield results than resistance training, although studies have reported beneficial effects on weight loss and body composition from both modes of
training (19). Still there are studies that did not report any changes with aerobic exercise, such discrepancies might be due to the different methods used to assess body composition (example, body mass index, weight, or fat mass), different modes of training, intensity and frequency of training and potentially the inclusion or lack of a dietary component to accompany the intervention. Even in the meta-analysis of controlled clinical trials by Normand et al there was no difference in the body compositions of control and experimental group (25).

8.5. Risk factors

Risk factors like hypertension, hyperlipidemia and improvement in blood lipid profile, increase in the sensitivity of insulin are proven benefits of aerobic exercise training. Many trials have shown the reduction in systolic and diastolic blood pressure to be in the range associated with prognostic benefit. Modest reduction in triglycerides and small increase in high-density lipoproteins are less clearly associated with prognostic benefit (19).

8.6. Effect of intensive glycemic control on neuropathy

A systematic review performed in 2012 which included randomized controlled trial (RCT) highlighted the positive effects of aggressive glycemic goals through the use of diet and exercise, oral hypoglycemic agents, insulin, or oral hypoglycemic agents plus insulin on neuropathy. Lifestyle interventions and medications significantly brought down the relative risk of foot ulceration in type 2 and type 1 diabetes. The authors concluded that enhanced glucose control significantly reduces nerve conduction and vibration threshold abnormalities. But the drawback in the high quality trial was that they were pragmatic in nature and aggressive therapies which included interventions like medications, diet, exercises (resistance and aerobic)
were heterogeneous in nature, hence it is difficult to analyze the type of intervention that really made a difference in terms of relative risk, risk difference, and mean difference between the conventional and treatment groups (72).

8.7. General guidelines for exercise in type 2 diabetes:

Before undergoing any exercise regime a pre-exercise evaluation is required to rule out diabetes related health complications. For individuals desiring to participate in low-intensity physical activity (PA) such as brisk walking, conducting exercise stress testing before walking is unnecessary and moreover no evidence suggests that it is routinely necessary as a CVD diagnostic tool, and requiring it may create barriers to participation among patient population (26).

8.8. Aerobic exercise training

Frequency: Aerobic exercise should be performed minimum of 3 days/week with interval not greater than 2 consecutive days between the exercise bouts. The Joint Position Stand by ADA and ACSM (American College of Sports Medicine) for exercise training recommends 5 days of exercise/week of moderate intensity in type 2 diabetes in adults (26).

Intensity: Aerobic exercises should be moderately intense at 40%-60% of VO$_2$ max or 40%-60% of heart rate reserve has been proved to be beneficial in controlling blood glucose and increasing insulin sensitivity in type 2 diabetes. For most of the people brisk walking may appear as moderately intense exercise which might be useful in controlling blood glucose levels. Added benefits are seen with vigorous exercises more than 60% of VO$_2$ max (26). A meta-analysis shows that individual who exercised at higher intensity seems to have better control of blood
glucose than individual who performed greater volume of exercises (27). Though higher intensity of exercise might not be tolerated by individuals of all the age-group affected by type 2 diabetes. Hence moderate intensity exercises play a pivotal role in the management of type 2 diabetes.

Table 6: Classification of exercise intensity, based on exercise lasting up to 60 minutes

| Intensity     | VO2R (%) | HRR (%) | % HR max | RPE | Resistance-Type Training*:
<table>
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<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Maximal Voluntary</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Contraction, % (1RM)</td>
</tr>
<tr>
<td>Very light</td>
<td>&lt; 20</td>
<td>&lt; 30</td>
<td>&lt; 10</td>
<td>&lt; 30</td>
<td></td>
</tr>
<tr>
<td>Light</td>
<td>20–39</td>
<td>35–54</td>
<td>10–11</td>
<td>30–49</td>
<td></td>
</tr>
<tr>
<td>Moderate</td>
<td>40–59</td>
<td>55–69</td>
<td>12–13</td>
<td>50–69</td>
<td></td>
</tr>
<tr>
<td>Hard</td>
<td>60–84</td>
<td>70–89</td>
<td>14–16</td>
<td>70–84</td>
<td></td>
</tr>
<tr>
<td>Very hard</td>
<td>≥ 85</td>
<td>≥ 90</td>
<td>17–19</td>
<td>≥85</td>
<td></td>
</tr>
<tr>
<td>Maximal</td>
<td>100</td>
<td>100</td>
<td>20</td>
<td>100</td>
<td></td>
</tr>
</tbody>
</table>

‡VO2R indicates oxygen uptake reserve; HRR- heart rate reserve; HR max-maximum heart rate; RPE- rating of perceived exertion; and 1RM is the maximum weight that can be lifted in 1 repetition.

†Adapted from the American College of Sports Medicine Position Stand (26)
**Duration:** The duration of the exercise prescription can be divided into the duration of each exercise session, as well as the period of training required to have a desired effect (19).

**Session duration:** Patients with type 2 diabetes should accumulate a minimum of 150 minutes of moderate-intensity exercise or 90 minutes of vigorous-intensity exercise each week [Evidence Level I (A)] (19). The duration of individual session may vary, although the aim should be a minimum of 10 minutes of exercise per session.

**Program duration:** Exercises have beneficial effects even in shorter duration regime. Exercises help in improvement of arterial stiffness and insulin resistance only after 3 weeks of aerobic training, despite the lack of measurable changes in anthropometric factors (body mass index or body fat). However the duration of exercise program may not be associated with changes in body mass index but at the same time it may be associated with decrease in insulin resistance, blood glucose control and lowering Cardio Vascular Disease (CVD) risk seen in type 2 diabetes (19).

**Mode:** Both aerobic and resistance training have important roles in type 2 diabetes. The combination of both forms of training was twice as effective for improving glycemic control (19). Any form of aerobic exercise (including brisk walking) that uses large muscle groups and causes sustained increases in HR is likely to be beneficial (26).

**Rate of progression:** At present, no study on individuals with type 2 diabetes has compared rates of progression in exercise intensity or volume. Gradual progression of both is advisable to minimize the risk of injury, particularly if health complications are present, and to enhance compliance (26).
8.9. Aerobic exercises in chronic peripheral neuropathies

There still remains dearth in literature regarding the role of aerobic exercises in modifying the natural progression of peripheral neuropathy. The studies reported are of poor methodological quality (73) and are inconclusive about the effect of aerobic exercise on DPN. The only study that has documented the effect of home based exercises on DPN was by Ruhland et al which lacked blinding and allocation concealment. Another study by Smith et al which followed up patients for a year found that diet plus exercise can result in partial cutaneous innervations (74). Unfortunately the study design was case control and had a poor methodological approach in the study.

8.10. Resistance exercises in type 2 diabetes

Resistance training is also growing therapeutic tool which has the potential to improve muscular strength, endurance, enhance flexibility, enhance body composition, and decrease risk factors for cardiovascular disease which are commonly encountered. A minimum of 8–10 exercises involving the major muscle groups should be performed with a minimum of one set of 10–15 repetitions to near fatigue. Increased intensity of exercise, additional sets, or combinations of volume and intensity may produce greater benefits and may be appropriate for certain individuals in type 2 diabetes. Therefore it is important that all individuals with type 2 diabetes should be carefully screened before beginning this type of training is initiated and they should receive proper supervision and monitoring during training. Caution should be used in cases of advanced retinal and cardiovascular complications (19, 25 and 27). Resistance training has been shown to induce a hypertrophic response and a muscle-fiber type shift in exercising muscles, which allows for a potential increase in whole body glucose utilization. A consequent increase in
GLUT4 proteins may in turn improve glycemic control. An increased capillary to-muscle ratio further favors improved glucose control. The use of resistance training to improve glycemic control in type 2 diabetes is supported by the American College of Sports Medicine (ACSM) and ADA position statements (26 and 75). Furthermore, the potential benefits of increases in muscle mass on body composition and other CVD risk factors have also been reported. Unlike aerobic training, higher intensities of resistance training (3 sets of 8 to 10 repetitions at 75% to 85% of 1 repetition maximum) have not only shown benefits but also have been well tolerated by patients with type 2 diabetes (19,26). However, for some patients, lower exercise intensities may be more appropriate.

8.11. Effect of diet in type 2 diabetes

Lifestyle modifications forms the cornerstone in the management of blood glucose levels and prevention of other complications like hypertension, higher levels of low density lipoproteins (LDL) or total cholesterol in the body. Meta-analysis of RCT on the use of dietary fibers in type 2 diabetes showed beneficial effects of dietary fibers on glycosylated hemoglobin with an overall mean decrease in HbA1c of 0.26% (24). A RCT investigating the effect of diet and physical activity on blood pressure and glucose concentrations (HbA1c) concluded that an intensive diet intervention soon after diagnosis can improve glycemic control at 6 months. Moreover, they found physical activity seems to have no added benefits in early lifestyle intervention (76).
8.11a. Carbohydrate and diabetes

The carbohydrates are usually defined as sugars, starch and fibers. A number of factors influence glycemic responses to foods, including the amount of carbohydrate, type of sugar, nature of the starch, cooking and food processing, and food form, as well as other food components. Though low glycemic index diet may reduce post-prandial hyperglycemia but the sustainability of these diets in long terms have not been established. Moreover, effect of carbohydrate diets on glycaemia and lipids appear to be modest only, with the long term effect of such interventions are questionable, as most of the studies are flawed and subject to criticism for the design (76).

8.11b. Fiber

Fiber diet in type 2 diabetes plays a vital role in the control of hyperglycemia. A variety of fiber-containing foods, such as whole grains, fruits, and vegetables, because they provide vitamins, minerals, fiber, and other substances which are important for good health. Recent studies have reported mixed effect of fibers on diabetes and lipid control. Ingestion of fibers in diet in large amount is cornerstone in the management of hyperglycemia and hyperinsulinemia, and elevated plasma lipids (76).

Though diet plays a modest role in the control of hyperglycemia but still there is a need to individualize the benefits of nutritional therapy for people with diabetes, with consideration of individual’s food and eating habits, metabolic profile, treatment goals, and desired outcomes (76).
8.12. Type 2 diabetes and yoga

Art of yoga is an ancient science of Indian mythology. Yoga programs usually train large muscle groups that results in increase in maximal oxygen uptake, decrement of sub maximal heart rate and augmentation of stroke volume. They also results in metabolic changes, such as reduction of blood lipid levels and decrease in blood lactate concentration during sub-maximal work (44). A systematic review on impact of yoga on type 2 diabetes concluded that there is a need of well-designed randomized controlled trials to assess the long term effectiveness of yoga on type 2 diabetes. It was further suggested that in future, trials of good methodological quality should be used with yoga as primary intervention for examining its effect on glycemia in type 2 diabetes. Apart from studying the long-term impact of yoga, there also appears a need to report a standardized mode or protocol for reporting data in trials involving yoga as a primary intervention (28).
Section 9

Pharmacological therapies in type 2 diabetes and neuropathy

DPN implies damage or loss of function of the peripheral nerves. Though there are a number of theories trying to postulate the exact mechanism for DPN, still there remains a dearth in literature as to exact cause for DPN. But it is clear that high glucose levels in the body changes the metabolism of nerve cells. Two main problems can result from loss or damage to the sensory nerve fibers. The first problem is loss of the sensation for pain. This increases the likelihood of ulcers in diabetic population. The second problem is a small fiber dysfunction seen in DPN which exhibits itself clinically as heightened sensation of pain and burning sensations that can be quite uncomfortable for the patient suffering from type 2 diabetes.

Good glycemic control usually halts or delays the onset of DPN but once a person gets diagnosed with DPN treatment options seems to be limited for the control of symptoms.

9.1. Antidepressants: Is a common form of drugs used for neuropathic pain.

Tricyclic antidepressants (TCAs): TCAs, such as desipramine and nortriptyline have proven to have beneficial effects. Yet, the most common adverse effects with tricyclic antidepressant use are the anticholinergic effects, which include dry mouth, blurred vision, constipation, urinary retention and cognitive impairment. Other serious side effects associated with these agents relate to cardiovascular toxicity and include orthostatic hypotension, tachycardia and changes in atrioventricular conduction (16).
Selective serotonin reuptake inhibitors (SSRIs) and serotonin/norepinephrine reuptake inhibitors (SNRIs): In a Cochrane review (Saarto & Wiffen, 2006) of antidepressant use in the management of neuropathic pain, the SSRIs, such as citalopram, paroxetine, sertraline and fluoxetine, were shown to have a little benefit (16).

Duloxetine hydrochloride is a reuptake inhibitor of 5-hydroxytryptamine and norepinephrine used to treat depression, generalized anxiety disorder, neuropathic pain, and stress incontinence in women. Duloxetine is also equally effective for the treatment of DPN and fibromyalgia.

9.2. Anticonvulsants

It is noticed apart from seizure management this group of drug is also effective in the management of pain.

Alpha 2 Delta Ligands

There have been seven randomized controlled trials of gabapentin in diabetic neuropathy. Four were placebo-controlled and three had active comparators. Three of the four placebo-controlled trials showed a statistically significant difference in pain, which was generally defined as at least a 50% reduction in pain. The fourth trial showed no benefit, but used the lowest dose of all the trials at 900 mg per day. Two studies compared gabapentin to amitriptyline, showing that gabapentin is at least as effective as amitriptyline (17).

The most common adverse effects noted to be associated with gabapentin use are related to the central nervous system. These include somnolence, ataxia and dizziness. Patients may also notice problems with gait or balance and experience gastrointestinal upset.
Pregabalin is a new alpha 2-delta ligand on the market and is the first agent to have been approved for the primary indication of neuropathic pain (16).

9.3. Opioids

Usually opioids are considered to be the last line of drugs for the treatment of DPN. There had been many studies on oxycodone (77) and the conclusion from the studies indicate that dosage of 10 to 60 mg can be safe and effective in the management of pain.

Though these benefits comes at the cost of adverse effects that are also seen on administration like constipation, nausea, vomiting and sedation are the most common ones and can greatly impact a patient’s productivity throughout the day. Physical dependence will also develop with chronic use and, therefore, it is important to reduce the dose of the agent slowly, if discontinuation is necessary, to avoid any symptoms of withdrawal (16).

9.4. Insulin and Oral Hypoglycemic Agents (OHA)

A systematic review comparing the role of insulin monotherapy and combination of insulin and oral hypoglycemic agents (metformin) found that the combination was better in controlling hyperglycemia than insulin or OHA alone. Combination therapy with bedtime insulin resulted in statistically significantly less weight gain compared to insulin monotherapy. However they found even when the patients had good control of their hyperglycemia in diabetes there were no significant differences in quality of life related issues (78).
Summary

Though for painful neuropathy drugs like TCA, anticonvulsants, opioids appear to be the mainstay of treatment for curing the symptoms of painful neuropathy, still their scope of practice clinically is very limited. In a systematic review of TCAs, anticonvulsants, opioids, and capsaicin cream, the evidence suggested that they are effective for management of acute pain in diabetic neuropathy in adults, although in most of the studies due to the side effects of the drugs treatment was discontinued (16).
### Table 7: Characteristics of important studies in the management of diabetic peripheral neuropathy

*(An overview)*

<table>
<thead>
<tr>
<th>Authors</th>
<th>Methods</th>
<th>Participants/studies</th>
<th>Intervention</th>
<th>Outcomes</th>
<th>Conclusion / Level of evidence</th>
</tr>
</thead>
</table>
| UK Prospective Diabetes Study [UKPDS] 1998 | *Design: RCT*  
*Allocation: concealed*  
*Blinding: blinded* | *Numbers*: 4209 patients  
*Age*: 25–65 years | Intensive glucose control with a sulfonylurea or insulin (*n=2729*) or conventional therapy with diet (*n=1138*) | Any diabetes-related end point, diabetes-related death, death from any cause, myocardial infarction, stroke, peripheral vascular disease, and microvascular disease | In patients with type 2 diabetes, the benefits of early intensive glucose control in preventing diabetes-related complications were sustained for up to 10 years.  
*Strength*: strong |
| Callaghan BC et al 2012        | *Systematic review*: Randomized controlled trials (RCTs) of enhanced glycemic control for type 1 and type 2 diabetes in which the presence or severity of peripheral neuropathy has been measured | *Numbers*: 47 studies met the inclusion criteria out of 470 studies | Frequent subcutaneous insulin administration, continuous insulin infusion, oral antidiabetic agents, lifestyle modifications such as diet and exercise, or pancreas transplant | Incidence of clinical neuropathy after at least one year | Enhanced glucose control significantly prevents the development of clinical neuropathy and reduces NCV & VPT abnormalities in type 1 diabetes. In type 2 diabetes, enhanced glucose control reduces the incidence of clinical neuropathy was unclear (*P = 0.06*).  
*Strength*: moderate |
| DCCT 1993                        | *Design: RCT*  
*Allocation: unclear*  
*Blinding: unclear* | *Numbers*: 1441 patients  
*Age*: age of 13 to 39 years Type 1 diabetes. | Either an external insulin pump or 3 or more daily insulin injections and guided by frequent blood glucose monitoring or conventional therapy with 1 or 2 daily insulin injections | Definite clinical neuropathy was defined as at least 2 of the following: physical symptoms, peripheral sensation, or decreased or absent reflexes  
NCV was done at baseline, 5th year and | Intensive therapy designed to normalize glucose levels prevented or slowed the progression of neuropathy in type 1 diabetes.  
*Strength*: moderate |
<table>
<thead>
<tr>
<th>Study</th>
<th>Design</th>
<th>Allocation</th>
<th>Blinding</th>
<th>Inclusion / exclusion criteria</th>
<th>Number</th>
<th>Age</th>
<th>Interventions</th>
<th>Outcomes</th>
<th>Strength</th>
</tr>
</thead>
<tbody>
<tr>
<td>Janet L Ruhland et al 1997</td>
<td>Design : RCT</td>
<td>Allocation: unclear</td>
<td>Blinding: unclear</td>
<td>Inclusion / exclusion criteria : unclear</td>
<td>Number: 28 participants</td>
<td>Age: 23-74</td>
<td>6 weeks exercise program</td>
<td>Average muscle score (AMS), handgrip force, forced vital capacity, and a timed 9.1-nl (30-ft) walk. The HRQL measure was the Medical Outcome Study (MOS), Short-Form Health (SF-36)</td>
<td>Home exercise program resulted in improvement of muscle force and SF-36 scores in individuals with chronic inflammatory demyelinating polyneuropathy.</td>
</tr>
<tr>
<td>Gordon Smith et al 2006</td>
<td>Design : case-control</td>
<td>Allocation: unclear</td>
<td>Blinding: unclear</td>
<td></td>
<td>Number: 32 participants (prediabetic)</td>
<td>Age: 52-68 years</td>
<td>Lifestyle interventions for 1 year</td>
<td>Skin biopsies, Visual analogue scale (VAS) for pain</td>
<td>Diet and exercise results in partial cutaneous innervation.</td>
</tr>
<tr>
<td>ACCORD 2010</td>
<td>Design: Parallel-group, randomized trial done in 77 clinical sites in North America</td>
<td>Allocation: concealed</td>
<td>Blinding: of participants was not possible and assessors were not mentioned</td>
<td></td>
<td>Number: 10,251 participants</td>
<td>Age: 55 to 79 years</td>
<td>Intensive Treatment( drug therapy) targeting a HbA1c concentration of &lt; 6.0% or standard treatment targeting HbA1c of 7.0% to 7.9%</td>
<td>New score of &gt; 2.0 on Michigan Neuropathy Screening Instrument</td>
<td>Accord 2010 reported lower risk of microvascular complications in the treatment arm but found hazard ratio greater in the treatment group.</td>
</tr>
</tbody>
</table>

**Adverse events:** DCCT, ACCORD and UKPDS reported adverse events of hypoglycemia with intensive therapy. The DCCT study (DCCT 1993a; DCCT 1993b) reported 62 episodes of hypoglycemia requiring assistance per 100 patient-years in the enhanced glucose control group, compared with 19 in the conventional group. Accord 2010 reported 538 events in 3.7 years of follow-up in intensively treated participants compared with 179 in the conventional group. The UKPDS Study Group 1998 group described a mean proportion of participants per year with one or more major hypoglycemic episodes of 1.0% of participants on chlorpropamide, 1.4% on glibenclamide, 1.8% on insulin, and 0.7% on diet.
Summary of the literature review

World health organization (WHO) estimates 60% of the diabetic population will be from developing countries in Asia by 2025 (79). Estimates of global diabetes prevalence and most recent projections for the future indicates that diabetes now affects 246 million people worldwide and is expected to affect some 380 million by 2025, representing as much as 7.1% of the global adult population (71). Prevalence of type 2 diabetes is progressively affecting middle aged and younger population worldwide. Most of the diabetics belong to developing countries with the age group of 40-60 years at a higher risk of developing diabetes. Currently India is not only the second most populated country of the world but has also been declared the diabetic capital of the world (79).

According to high-quality evidences, enhanced glucose control in type 1 diabetes significantly reduces the annual development of clinical neuropathy and produces small, but significant improvements in peroneal and median motor nerve conduction velocity and vibration detection threshold. However In type 2 diabetes, high-quality evidences suggest that the reduction in the annual development of neuropathy with enhanced glucose control was statistically insignificant. Importantly, there was a large increased risk of adverse events with enhanced glucose control in both types of diabetes. Trials like DCCT, ACCORD and UKPDS reported major adverse events with intensive therapy, like mortality and episodes of hypoglycemia requiring assistance in form of hospitalizations.