CHAPTER 1

1.1. INTRODUCTION

Diabetes mellitus is a metabolic disorder and is characterized by hyperglycemia resulting from defects in insulin secretion, insulin action or both (Atkinson et al 1994). Indians are genetically more susceptible to diabetes and the World Health Organization predicts the number of diabetic persons in India would go up to 40 million by 2010 and to 74 million by 2025. (Pillai, 2006) It is also estimated that there are about 30 to 33 million diabetic patients in India and every fourth diabetes patient in the world today is an Indian.

Diabetes is one among the major healthcare problem in India. According to Diabetes Atlas published by the International Diabetes Federation (2005 IDF), the countries with the largest number of diabetic people would be India, China and USA by 2030. Due to these increasing numbers, the economic burden due to diabetes in India is amongst the highest in the world. The real burden of this disease is however due to its associated complications which lead to increased morbidity and mortality.

WHO estimated that mortality from diabetes, heart disease and stroke costs about $210 billion in India, much of the heart disease and stroke in these estimates were associated with diabetes. WHO estimates that over the next 10 years in India about $ 333.6 billion will be spent for treating diabetes, heart disease and stroke.

An increased economic and urbanized life style has produced advancement in developing countries such as India which has resulted in dramatic lifestyle changes leading to lifestyle related diseases like diabetes. The transition from a traditional to modern lifestyle, consumption of fast food diets rich in fat and calories combined with a high level of mental stress has compounded the problem further. There are several studies
from various parts of India which reveal a rising trend in the prevalence of type II diabetes in the urban areas. (Ramachandran et al 2011) A National Urban Survey in 2000 observed that the prevalence of diabetes in urban India in adults was 12.1 per cent. Recent data has illustrated the impact of socio-economic transition occurring in rural India. The transition has occurred in the last 15 years and the prevalence has risen from 2.4 per cent to 6.4 per cent.

Development of diabetes in Indians takes place at very young age, at least 10 to 15 years earlier than the western population. Early occurrence of diabetes gives ample time for development of the chronic complications of diabetes. In India, the life span of people has increased hence more number of people with diabetes are being detected. The prevalence of diabetes increases with a family history of diabetes also. A high incidence of diabetes is seen among the first degree relatives. Indians have a high genetic risk for diabetes as observed in Asian Indians, who have migrated to other countries (Verma et al 1989), they have been found to have a higher rate of diabetes as compared to the local population. The association of obesity also with Type II Diabetes is well known. Even with an acceptable body weight range, weight gain could increase the risk of diabetes. An excess of body fat specially concentrated within the abdomen has an increased risk of diabetes. The cut-off limits for waist circumference for Indians have been recommended to be 90 cm for males and 80 cm for females. Abdominal obesity is defined by waist circumference above these limits.

Extensive evidences prove that Physical inactivity and lack of exercises also plays a major role for the development of type II Diabetes. Usage of motorized vehicles for transportation and change in work patterns with machines and a shift in occupations combined with sophisticated life style has reduced the physical activity in all groups of
populations. Asian Indians have been found to be more insulin resistant as compared to the white population. They have a higher level of insulin to achieve the same blood glucose control. A group of factors consisting of abnormal fats, high blood pressure, obesity, and abnormal glucose levels known as metabolic syndrome is highly prevalent in Asian Indians. The impact of stress on physical and mental well being along with the lifestyle changes has a strong effect on increasing the incidence of type II Diabetes amongst persons with strong genetic background. (Gupta et al 2001)

Ample evidence suggests that preventive measures to reduce the burden of diabetes are needed. The US Diabetes Prevention Programme, the Finnish Diabetes Prevention Programme and the Chinese Study have conclusively proved that lifestyle modification including weight loss, increased physical activity and dietary changes can prevent or delay the onset of diabetes. The need of the hour is direct public education and mass media campaigns, awareness programs about diabetes and its complications like diabetic neuropathy (Somannavar et al 2008). There is a need to spread the message that diabetes and its complication is preventable and a behavioral change is needed to adopt a healthy lifestyle.

Diabetes affects all the systems of the body among which its impact over peripheral nerve is severe leading to diabetic neuropathy which produces neuropathy pain, sensory loss, weakness and others. Peripheral nerve dysfunction is a common complication of human Diabetes mellitus (Clements et al 1979, Sidenius et al 1982). Clinical symptoms of peripheral neuropathy are present in approximately 25% of diabetic individuals, while nearly all diabetics have a reduction of nerve conduction velocity (Campbell et al 1976, Spritz et al 1978).
Peripheral nerve pathology in diabetic neuropathy is characterized by the axonal atrophy and degeneration. Segmental demyelination, hypertrophy and proliferation of Schwann cells are occasionally observed, but these changes are thought to be secondary to the axonal involvement (Medori et al 1985). Several mechanisms have been considered to explain the pathogenesis of the diabetic polyneuropathy (Greene et al 1985). The most important factors to note is that axonal atrophy and degeneration are secondary to an impairment of axonal transport, caused by metabolic defects due to diabetes (Sidenius et al 1982).

The development of the most common form of diabetic neuropathy the distal symmetrical Polyneuropathy, is thought to be caused by some chronic metabolic disturbance and recent pathological studies seem to exclude occlusive vascular disease as a primary causative factor. (Greene et al 1985) However, the importance of insulin deficiency in the pathogenesis of diabetic neuropathy is still disputed because of positive and negative data concerning the relationship between the degree of antecedent 'diabetic control" and the development of this syndrome, and the response to insulin treatment in patients with diabetic neuropathy.

Patients with diabetic polyneuropathy exhibit decreased peripheral motor and sensory nerve conduction velocities, and similar alterations have been found in long-standing diabetics who have no evidence of polyneuropathy, in both of these instances the decreased nerve conduction velocities are associated with lesions in peripheral nerve biopsies, which are more marked in the patients with polyneuropathy. These lesions include loss of myelinated axons, evidence of segmental demyelination and remyelination, and in some instances Schwann cell proliferation (Chopra et al 1969).
Quan et al (2010) stated that the Peripheral neuropathies have been described in patients with primary and secondary diabetes of diverse causes, suggesting a common etiologic mechanism based on chronic hyperglycemia. Pathologically, numerous changes have been demonstrated in both myelinated and unmyelinated fibers. Diabetic peripheral neuropathy is a common complication of diabetes that can cause significant morbidity and mortality. Around 30% of hospitalized and 20% of community-dwelling diabetes patients has peripheral neuropathy; the annual incidence rate is approximately 2% (Duby et al 2004).

**Diabetic Neuropathy**

Diabetic neuropathy is very heterogeneous, and can be broken down into a number of mono- and polyneuropathies as well as plexopathies and radiculopathies. Neuropathies are characterized by a progressive loss of nerve fibers that can be assessed noninvasively by several tests of nerve function, including nerve conduction studies and electromyography, quantitative sensory testing, and autonomic function tests. A widely accepted definition of diabetic peripheral neuropathy is "the presence of symptoms and/or signs of peripheral nerve dysfunction in people with diabetes after the exclusion of other causes." (Boulton et al 1998).

Diabetic neuropathy is classified into several syndromes, each with a distinct pattern of involvement of peripheral nerves. Patients often have multiple or overlapping syndromes. Sensorimotor neuropathy is marked by pain, paresthesia, and sensory loss. Cardiac autonomic neuropathy (CAN) may contribute to myocardial infarction, malignant arrhythmia, and sudden death. Gastroparesis is the most debilitating complication of gastrointestinal autonomic neuropathy. Genitourinary autonomic neuropathy can cause sexual dysfunction and neurogenic bladder. The pathology of diabetic neuropathy
involves oxidative stress, advanced glycation end products, polyol pathway flux, and protein kinase C activation all contribute to micro vascular disease and nerve dysfunction.

1.2. PATHOPHYSIOLOGY OF DIABETIC NEUROPATHY:

Micro vascular Factor

Peripheral nervous system and Micro vascular systems are inseparable by their physiological interdependence. In the simplest terms, blood vessels depend on neural regulation for normal function, and neurons depend on capillaries for nutrients. The self-perpetuating potential of Micro vascular and neural dysfunction in the development of diabetic neuropathy is supported by a number of influential studies. (Duby et al 2004). Most of the literature refers to diabetic neuropathy as a Microvascular complication or Neurovascular disease. Diabetic neurovascular disease is a disorder of metabolism, and the major factor for pathogenesis is either vascular or nervous tissue which requires insulin for the glucose uptake. Hence, hyperglycemia causes elevated intracellular glucose levels which drive secondary pathologies like oxidative stress and protein glycation which remains same in both vascular and nervous tissue. However, although the systems are interdependent and may have similar diabetic pathologies, they are unique, especially with respect to the challenges of treatment.

The first pathological change in the micro vascular structure is a physiological shift favoring vasoconstriction, evidenced by blunted vasodilatation and elevated vasoconstrictor activity (Cameron et al 2001). As the disease progresses, neuronal dysfunction correlates closely with the development of vascular abnormalities, such as capillary basement membrane thickening and endothelial hyperplasia, which contribute to diminished oxygen tension and hypoxia(Gianni et al 1995, Timperley et al 1997).
Indeed, hemodynamic abnormalities, hypo perfusion, and neuronal ischemia are well-established characteristics of diabetic neuropathy (Cameron et al 2001, Sheetz et al 2002). Finally, diabetic animal models have demonstrated that vasodilator agents (e.g., Angiotensin-converting-enzyme [ACE] inhibitors, alpha1-antagonists) and experimental drugs (e.g., Aldose reductase inhibitors, PKC inhibitors) can lead to substantial improvements in the neuronal blood flow, with corresponding improvements in NCV (Cameron et al 2001). Thus, micro vascular dysfunction occurs early in diabetes, parallels the progression of neural dysfunction, and may be sufficient to support the severity of structural, functional, and clinical changes observed in diabetic neuropathy.

**Oxidative Stress**

High increase in the production of free radicals in diabetes may be harmful by several mechanisms which are not still fully understood. They include direct damage to the circulatory vessels leading to ischemia of nerve and facilitation of AGE reactions (Advance Glycation End products). Despite the incomplete understanding of these processes, use of the antioxidant alpha lipoic acid may improve neuropathic symptoms. The role of oxidative stress as a result of reactive oxygen species has been studied through the use of taurine. This antioxidant has been shown to attenuate nerve conduction deficits and nerve blood flow deficits in rats with streptozotocin-induced diabetes (Yagihaskhi et al 2001), and also to counteract oxidative stress and nerve growth factor deficits in these animals (Pop Basui et al 2001).

Neuropathy in diabetes may also be at least partly caused by impairment of nerve fiber regeneration, a mechanism supported by abnormalities of the early gene responses necessary for initiating nerve fiber regeneration after sciatic nerve crush injury in a spontaneously diabetic rat model (Obrosava et al 2001). The calcium and sodium
channels also appear to play important roles. In diabetic rats, the impaired regulation of calcium channels leads to enhanced calcium influx in sensory neurons (Xu et al 2001), and there is up regulation of the b3 subunit of the sodium channel (Shah et al 2003). Problems that are a consequence of or co-contributors to these disturbed biochemical processes include the altered gene expression with altered cellular phenotypes, changes in cell physiology relating to an endoskeletal structure or cellular transport, reduction in neurotropins, and nerve ischemia. In the case of focal or asymmetrical diabetic neuropathy syndromes, vascular injury or autoimmunity may play more important roles.

Diabetes is foremost a hypermetabolic state, that promotes elevated intracellular concentrations of glucose that can participate in a number of different pathological processes. Sugars can react with reactive oxygen species to form carbonyls that can further react with proteins or lipids to produce glyoxidation or lipioxidation compounds, respectively (Baynes et al 1999). Glucose and its metabolites can also create carbonyl complexes with proteins directly, producing AGEs that contribute to oxidative stress as well. Ultimately, glucose metabolism itself creates free-radical byproducts in the normal production of ATP. The presence of excessive glucose may lead to an increased production of reducing agents (i.e., NADH and FADH2) through glycolysis and the tricarboxylic acid cycle (Brownlee et al 2001). The surplus amount of electron donors may result in a dangerous imbalance in the mitochondrial electron transport chain that could accelerate the production of superoxide, a highly reactive free radical (Brownlee et al 2001). In summary, oxidative stress describes an increase in substrate for AGEs, an increase in precursors for glyoxidation and lipioxidation products, and acceleration in free-radical formation that may be accompanied or caused by a deficiency of the antioxidant and detoxification pathways (Baynes et al 1999).
Glycoxidation and lipoxidation products represent an extensive and diverse group of potentially deleterious compounds. Superoxide anion is capable of profound tissue damage and may contribute to the activation of PKC by inducing de novo synthesis of diacylglycerol (Nishikawa et al 2000). In fact, the existing evidence of oxidative stress supports a number of expert hypotheses, ranging from a unifying pathology to a universal consequence of disease itself (Baynes et al 1999, Brownlee et al 2001). However, a principal role for oxidative stress in the pathology of diabetic neuropathy currently hinges on gaps in basic research and disappointing clinical trials. Tissue concentrations of known carbonyl compounds are nearly negligible, and the antioxidants have been shown to be of little benefit for the treatment of diabetic neuropathy or microvascular disease (Baynes et al 1999, Sheetz et al 2002).

**AGES (Advance Glycation end products):**

The non enzymatic reaction of excess glucose with proteins, nucleotides, and lipids results in advance glycation end products that may have a role in disrupting neuronal integrity and repair mechanisms through interference with the nerve cell metabolism and axonal transport (Vinik et al 1999).

Glucose and other sugars in non-enzymatic form covalent bonds with proteins through the Maillard reaction to produce Schiff bases and Amodori products, which can further degrade or react to produce AGEs. This process occurs in euglycemic individuals and normally affects only longer-lived proteins, but hyperglycemia provides an excess of substrate (i.e., glucose) that may accelerate the reaction, with pathological consequences. The glycation of essential proteins could alter their structure and impair their function (Vlassara et al 2002). There is scattered evidence linking AGEs to abnormalities in the vascular tissue, lipid metabolism, and the platelets that may lead to the pathology of
diabetic neuropathy (Vlassara et al 2002). Receptors for AGEs have also been identified that can contribute to oxidative stress and activate signal-transduction pathways, such as PKC and Mitogen-activated protein (Brownlee et al 2001, Dickson et al 2002). Potent AGE cross-link inhibitors such as Amino Guanidine, have demonstrated the efficacy in preventing diabetic vascular complications in animal models, but their lack of efficacy and dose-limiting toxicity have proven to be prohibitive in humans (Brownlee et al 2001, Sheetz et al 2002, Vlassara et al 2002).

**Polyol Pathway Flux**

Hyperglycemia causes increased levels of intracellular glucose in nerves, leading to the saturation of the normal Glycolytic pathway. Extra glucose is shunted into the polyol pathway and converted to Sorbitol and fructose by the following enzymes, Aldose reductase and Sorbitol dehydrogenase. Accumulation of Sorbitol and fructose lead to reduced nerve Myoinositol, decreased membrane Na⁺/K⁺, ATP activity, impaired axonal transport, and structural breakdown of nerves, causing abnormal action potential propagation. This is the rationale for the use of Aldose reductase inhibitors to improve nerve conduction.

The polyol pathway provides persuasive indications that the unifying feature of chronic hyperglycemia can induce and drive subordinate metabolic processes that promote intracellular instability and decay. It is essentially an alternative catabolic pathway that is activated and supplied by elevated intracellular glucose levels (Du et al 2000, Oates et al 2002). The first redox reaction of the polyol pathway couples the reduction of glucose by the enzyme al-dose reductase with the oxidation of NADPH to NADP⁺, producing sorbitol. Sorbitol is further oxidized to fructose by sorbitol dehydrogenase, which is coupled with the reduction of NAD⁺ to NADH. It was once believed that the
accumulation of sorbitol resulted in osmotic stress that caused neuron damage, but it is generally accepted that sorbitol concentrations are relatively insignificant in the nerves and vascular tissue of patients with diabetes (Sheetz et al 2002, Brownlee et al 2001, Oates et al 2002). The current hypothesis holds that a high rate of "flux" of glucose through the polyol pathway is pathogenic, primarily by increasing the turnover of cofactors -- NADPH and NAD$^+$. The reduction and regeneration of glutathione require NADPH, and depletion of glutathione could contribute to oxidative stress and the accumulation of toxic species (Oates et al 2002). Also, when an imbalance in the NADH: NAD$^+$ ratio could ultimately result in increased production of AGEs and the activation of diacylglycerol and PKC. Aldose reductase inhibitors are effective in preventing the development of diabetic neuropathy in animal models. However, human trials have demonstrated disappointing results and dose-limiting toxicity. Investigators continue to search for a potent inhibitor with adequate tissue penetration and a tolerable adverse-effect profile (Oates et al 2002).

The role of polyol pathway abnormalities is supported by a recent study using mice with streptozotocin-induced diabetes who were made transgenic for human aldose reductase, and who were found to have slowed nerve conduction velocities, more severe nerve fiber atrophy, and higher levels of sorbitol and fructose in peripheral nerves than non-transgenic mice (Uehara et al 2004).

**PKC**

There is mounting evidence that PKC may be a critical conductor in the metabolic pathologies associated with diabetic neuropathy. The term "PKC" actually describes a super family of 12 isoenzymes that act in the transduction of intracellular signaling and are activated by phosphorylation and subsequent binding to the second messenger
diacylglycerol (Sheetz et al 2002, Eichelberg et al 2002). Elevated intracellular glucose has been linked to increased diacylglycerol and PKC levels in retinal, aortic, and renal tissues, but, surprisingly, neuronal concentrations of diacylglycerol and PKC appear to be largely unchanged or even decreased under diabetic conditions. However, studies have demonstrated that PKC inhibitors can improve Na\(^+\)-K\(^+\) ATPase activity, which is suppressed and could contribute to diminished NCV in diabetes (Eichelberg et al 2002). More important, beta\(_1\) - and beta\(_2\)-specific PKC inhibitors have been shown to be capable of preventing diminished neuronal blood flow and NCV in diabetic animal models.

1.3. **CLINICAL SYMPTOMS OF DIABETIC NEUROPATHIES:**

In type 1 diabetes mellitus, distal polyneuropathy typically becomes symptomatic after many years of chronic prolonged hyperglycemia. Conversely, in type 2, it may present after only a few years of known poor glycemic control. Sometimes patients with type 2 Diabetes mellitus may already have neuropathy at the time of diagnosis.

Since diabetic neuropathy can be manifested with a wide variety of sensory, motor, and autonomic symptoms, a structured list of symptoms can be used to help screen all diabetic patients for possible neuropathy.

Sensory symptoms may be negative or positive, diffuse or focal. Negative sensory symptoms include feelings of numbness or deadness, which patients may describe as being akin to wearing gloves or socks. Loss of balance, especially with the eyes closed, and painless injuries due to loss of sensation are common. Positive symptoms may be described as burning, prickling pain, tingling, electric shock-like feelings, aching, tightness, or hypersensitivity to touch.
Motor problems may include distal, proximal, or more focal weakness. In the upper extremities, distal motor symptoms may include impaired fine hand coordination and difficulty with tasks such as opening jars or turning keys. Foot slapping and toe scuffing or frequent tripping may be early symptoms of foot weakness. Symptoms of proximal limb weakness include difficulty climbing up and down stairs, difficulty getting up from a seated or supine position, falls due to the knees giving way, and difficulty raising the arms above the shoulders. In the most common presentation of diabetic neuropathy with symmetrical sensorimotor symptoms, minor weakness of the toes and feet may be seen, but severe weakness is uncommon and should prompt investigation into other causes, such as Chronic Inflammatory Demyelinating Polyradiculoneuropathy (CIDP), or Vasculitis. More severe weakness may be observed in asymmetrical diabetic neuropathy syndromes.

Autonomic symptoms may be sudomotor (dry skin due to lack of sweating or excessive sweating in defined areas), pupillary (poor dark adaptation, sensitivity to bright lights), cardiovascular (postural lightheadedness, fainting), urinary (urgency, incontinence, dribbling), gastrointestinal (diarrhea, constipation, nausea, or vomiting), and sexual (erectile impotence and ejaculatory failure in men, loss of ability to reach sexual climax in women).

A generally accepted classification of diabetic neuropathies divides them broadly into symmetric and asymmetric neuropathies. Development of symptoms depends on the total hyperglycemic exposure and other risk factors such as elevated lipids, blood pressure, smoking, increased height, and high exposure to other potentially neurotoxic agents such as ethanol. Establishing the diagnosis requires careful evaluation since patients with diabetes may have neuropathy from another cause. Depending on the physician practices
studied, this group may represent 10-26% of diabetic patients with neuropathy (Quan et al 2010).

**Symmetric Polyneuropathies:**
Symmetric polyneuropathies involve multiple nerves diffusely and symmetrically.

**Distal Symmetric Polyneuropathy**
This is one of the most common manifestations of diabetic neuropathy. Sensory, motor, and autonomic functions are affected in varying degrees, with sensory abnormalities predominating than the motor impairment. Peripheral nerves are affected in a length-dependent pattern (the longest nerves affected first) which causes chronic symmetrical symptoms. Clinical symptoms commonly presents as painful paresthesias and numbness, which begin in the toes and ascend proximally in a stocking like distribution which progress over months to years. Sensory disturbances starts distally in lower extremity and when sensory symptoms reach the knees, the hands also develop similar symptoms, progressing proximally in a glove like distribution, anterior aspect of the trunk and vertex of the head may be affected at a very late stage. Mild weakness of foot muscles and decreased ankle and knee reflexes can also occur commonly. Loss of the foot sensation can predispose to the development of foot ulcers and gangrene with impaired Proprioception and vibratory perception; gait may be affected (sensory ataxia).
**Small-fiber Neuropathy**

This is another form of symmetric neuropathy with distal symmetrical neuropathy involving predominantly small-diameter sensory fibers (A delta and C fibers) which manifests as painful paresthesias that patients perceive as burning, stabbing, crushing, aching, or cramp like, with increased severity at night. Loss of pain and temperature sensation with relative sparing of distal reflexes and proprioception can also be noted in this type of neuropathy.

**Diabetic Autonomic Neuropathy**

Pure autonomic neuropathy is a rare type and some degree of autonomic involvement is seen in most patients with diabetic polyneuropathy. The clinical signs may include orthostatic hypotension, resting tachycardia, loss of sinus arrhythmia, anhydrosis, bowel or bladder dysfunction, and small pupils sluggishly reacting to light.

**Diabetic Neuropathic Cachexia**

This type of neuropathy manifests with precipitous and profound weight loss followed by severe and unremitting cutaneous pain, small-fiber neuropathy, and autonomic dysfunction which occurs more often in older men; impotence is one of common the symptom in this condition and the symptoms can be improved with prolonged glycemia control. Symptoms are often refractory to other pharmacologic treatment and limited anecdotal improvement is reported with non pharmacologic treatments such as sympathectomy, spinal cord blockade, and electrical spinal cord stimulation. Recovery may be incomplete and can prolong over many months following any form of treatment.
Asymmetric Neuropathies:

Asymmetric Neuropathies include single or multiple cranial or somatic mononeuropathies. Syndromes include median neuropathy of the wrist (carpal tunnel syndrome), single or multiple somatic mononeuropathies, thoracic radiculoneuropathy, lumbosacral radiculoplexus neuropathy, and cervical radiculoplexus neuropathy. These syndromes are distinguished from typical distal diabetic polyneuropathy by the following characteristics:

1. They often have a monophasic course,
2. Some are associated with inflammatory angitis and ischemia (eg, lumbosacral radiculoplexus neuropathy) and may appear acutely or subacutely.
3. They have a weaker association with total hyperglycemic exposure than symmetrical polyneuropathies.

Cranial Mononeuropathy

Cranial nerves (CN) III, IV, VI, VII, and II are most often involved in this type of mononeuropathy. CN III, IV, and VI disease manifests as acute or subacute periorbital pain or headache followed by diplopia, Muscle weakness is seen typically in the distribution of a single nerve, and pupillary light reflexes are usually spared and complete spontaneous recovery usually occurs within 3 months. Facial neuropathy manifests as acute or subacute facial weakness (taste is not normally involved) and can be recurrent or bilateral and most recovery occurs spontaneously in 3-6 months. Anterior ischemic optic neuropathy manifests as acute visual loss or visual field defects (usually inferior altitudinal). In this condition the optic disk appears pale and swollen; flame-shaped hemorrhages may be present.
Somatic Mononeuropathies

Focal neuropathies in the extremities are caused by entrapment or compression at common pressure points or by ischemia and subsequent infarction. Entrapment and compression tend to occur in the same nerves and at the same sites as in individuals without diabetes. Median Nerve entrapment at the wrist (carpal tunnel syndrome) is more common in patients with diabetes and can be treated in the same manner as in patients without diabetes. Neuropathy secondary to nerve infarction presents acutely with focal pain associated with weakness and variable sensory loss in the distribution of the affected nerve. Multiple nerves may be affected (mononeuritis multiplex).

Diabetic thoracic Radiculoneuropathy

This type of diabetic neuropathy presents with burning, stabbing, boring, belt-like, or deep aching pain usually begins unilaterally; then may become bilateral. Skin hypersensitivity and allodynia (Pain with normally innocuous touch) may occur with numbness in a dermatomal distribution, most prominent in distal distribution of intercostal nerves.

In this case Single or multiple spinal roots are involved and Contiguous territorial extension of symptoms may occur in a cephalad, caudal, or contralateral direction. Thoraco-abdominal neuropathy or radiculopathy may cause chest and/or abdominal pain in the distribution of thoracic and/or upper lumbar roots. Weakness presents in the distribution of the affected nerve root, eg, bulging of the abdominal wall from abdominal muscle paresis (thoracic root). Patients older than 50 years are affected most often; it is more common in diabetes mellitus type 2 and is often associated with significant weight loss. Coexisting diabetic distal symmetrical polyneuropathy often is present.
Diabetic Radiculoplexus neuropathy

The syndrome may occur in the cervical or lumbosacral distributions and is referred to in the literature by various designations including diabetic amyotrophy, Bruns-Garland syndrome, and diabetic plexopathy, among others. The most frequent initial symptom is sudden, severe, unilateral pain in the hip/lower back or shoulder/neck. Weakness then develops days to weeks later. Atrophy of the limb musculature may occur. Allodynia, paresthesias, and sensory loss are common. Symptoms usually begin unilaterally and may later spread to the opposite side. Reflexes in the affected limb may be depressed or absent. This condition often occurs in patients older than 50 years with poorly controlled diabetes. It is more common in men than in women. Significant weight loss occurs in 50% of patients. The course is generally monophasic with improvement over many months; however, some residual deficits often remain.

1.4. ASSESSMENT OF NEUROPATHY

The first clinical sign that usually develops is decrease or loss of vibratory and pin prick sensation over the toes (Simmons et al 2000). As disease progresses, the level of decreased sensation may move upward into the legs and then into the hands and arms, a pattern often referred to as "stocking and glove" sensory loss. Very severely affected patients may lose sensation in a shield distribution on the chest. Deep tendon reflexes are commonly hypoactive or absent and weakness of small foot muscles may develop. More focal findings may be seen with injury to specific nerves as described above.

There are many ways to assess neuropathy. For screening large numbers of diabetic patients, inexpensive, rapid methods are useful. Two common methods used are the monofilaments to measure touch sensitivity (Armstrong et al 1998, Muller et al 1996) and the use of tactile circumference discrimination (Maser et al 1997, Vileikyte et al 1997)
Another very useful tool is the Michigan Neuropathy Screening Instrument, an eight-point assessment that relies on clinical examination of the feet, the presence or absence of foot ulcerations, the assessment of vibratory sensation in the great toes, and grading of ankle reflexes (Feldman et al 1994). A technique that has recently been studied is tactile directional sensibility, a quantitative form of which was found to have high sensitivity and specificity for neuropathy (Norsell et al 2001). However, this technique requires specialized equipment, and it is unclear that it offers a clear advantage over conventional techniques. For clinical trials, nerve conduction studies are often used, and are shown to be symmetrical in patients with diabetic sensory and sensorimotor polyneuropathy, thus justifying unilateral evaluation (Perkins et al 2002). Another method of assessment is symptom quantitation using instruments such as the Neuropathy Symptom Score (Dyck et al 1993) and Neuropathy Symptom Profile (Dyck et al 1986). It has been pointed out that positive sensory symptoms (prickling, tingling, sensations, burning, aching, throbbing, etc.) are usually the primary clinical concern of patients, and should be considered endpoints for epidemiological studies and controlled clinical trials (Apfel et al 1999). The quality of life may also be assessed, particularly in view of the relationship between conventional measurements of neuropathy and quality of life. In clinical trials involving animal models assessment of neuropathy is done by motor & sensory nerve conduction velocities as golden standard. The measurement of the H-wave amplitude was recently found to be of value and motor functional analysis also done on measuring walking track analysis, and sensory function assessed by extensor thrust reflex etc..
1.5. MEDICAL MANAGEMENT FOR DIABETIC NEUROPATHY

The treatment of diabetic neuropathy may be classified as primary prevention, symptom management, and disease modifying. The Diabetes Control & Complication research group (1993) and the UK Prospective Diabetes Study group (1998) demonstrated that the risk of neuropathy and other complications can be dramatically reduced or delayed by intensified glycemic control in patients with type 1 and 2 diabetes. These results are especially important in light of the fact that treatments directed at symptom management are polypharmacy nightmares fraught with adverse effects and are only moderately effective. Disease modifying agents, which target the underlying pathologies, have a disappointing history but remain the critical focus of secondary intervention and are a hope for the near future.

Symptom management typically requires careful use of a combination of agents. Current evidence from clinical trials supports the use of desipramine, amitriptyline, capsaicin, tramadol, gabapentin, bupropion, and venlafaxine as preferred medications for the treatment of diabetic sensorimotor neuropathy. Citalopram, NSAIDs, and opioid analgesics may be used as adjuvant agents. Lamotrigine, oxcarbazepine, paroxetine, levodopa, and alpha-lipoic acid are alternative considerations. The evidence supporting the use of zonisamide, fluoxetine, mexiletine, dextromethorphan, and phenytoin is considered equivocal, and their risks are generally better defined than their benefits.

Diabetic autonomic neuropathy is extremely difficult to treat, and the risks and adverse effects frequently outweigh the benefits of most pharmacologic therapies. The symptoms of CAN may be ameliorated with fludrocortisone, clonidine, midodrine, dihydroergotamine or caffeine, octreotide, ACE inhibitors, and beta-blockers. Gastroparesis may be improved with metoclopramide or erythromycin, but glycemic
control is perhaps the best long-term treatment. Erectile dysfunction may respond to phosphodiesterase inhibitors, vacuum-constriction devices, and intracavernosal injections.

It is critical that all clinical recommendations be based on a thorough patient review to minimize potentially severe adverse effects. Further, all medications should be initiated at low dosages and adjusted to individual efficacy and adverse effects. Ruboxistaurin represents the current hope for future disease-modifying therapies. Glycemic control remains the foundation of prevention and the prerequisite of adequate treatment of diabetic neuropathy.

1.6. PHYSIOTHERAPY INTERVENTIONS FOR MANAGING DIABETIC NEUROPATHY

For Functional Improvement and Pain

Diabetic neuropathy is a painful condition, so the thought of physiotherapy may not seem appealing, as it involves movement (Nussbaum et al 2006). However, physiotherapy will help to regain motions that have been lost or to improve patients balance when walking. This may include the use of braces and splints as well as exercise machines. Treatments will focus on maintaining and improving the patient’s range of motion, as well as strengthening their muscles. For example, something as simple as learning how to stand without getting dizzy is also a part of diabetic neuropathy physiotherapy. Patients can also be trained to maneuver over different surfaces to avoid tripping and falling when patients go about their everyday activities. Improving the balance, which may have worsened with neuropathy can also be trained with physiotherapy. Splints and braces will also be included as part of physical therapy. Using wrist splints can help to learn and use of proper techniques when picking up or grabbing objects. Back braces are also recommended by Physiotherapist to enhance correct posture to help combat pain caused
by nerve damage (Nussbaum et al 2006). The physiotherapist may utilize a direct approach, attacking the problem leading toward the functional deficit, or work indirectly, circumventing the underlying problem and focusing on a compensatory strategy. A good physiotherapist will utilize all available equipment, modalities, and therapeutic exercise to aid in every patient’s functional progress. Each patient may react differently to this therapeutics; careful progression over time will prove to be fundamental in successful treatment. Therapists may draw from the following range of equipments and therapeutic modalities to provide each patient with the best chance of pain-free, independent functionality.

- Skilled soft tissue techniques
- Peripheral and spinal mobilizations
- Thermal modalities
- Electrical stimulation
- Ultrasound
- Vibration platforms
- Near infrared phototherapy
- Balance systems and force plates
- Individualized therapeutic exercise
- Functional activities

Consulting an expert physiotherapist can help give each patient a chance at the most positive outcome for functional improvements.

Electrostimulation has been shown to provide temporary relief of pain associated with diabetic sensorimotor neuropathy, but the feasibility and efficacy of maintenance therapy remain controversial. A randomized study on transcutaneous electrotherapy involved 31 patients with diabetic peripheral neuropathy to take a portable electrotherapy machine
home for one week of self-administration (Kumar et al 1997). Patients were assigned to therapy with either active or inactive electrodes. The therapy for both groups consisted of placing electrodes as instructed and administering electrical shock for 30 minutes every day. Active therapy improved neuropathic symptoms in 15 (83%) of the 18 patients, compared with 5 (38%) of 13 patients receiving sham therapy. No major adverse effects were observed in either group. The therapy had a very low residual effect, and patients' pain returned within one week of stopping treatment.

In a related study, Percutaneous electrical nerve stimulation (PENS) was examined for value in the treatment of painful diabetic neuropathy (Hamza et al 2000). Therapy consisted of using 10,32-gauge "acupuncture-like" needles to puncture the soft tissue and muscle of the foot and leg to a depth of 1-3 cm and applying alternating frequencies of electrical shock. The crossover design randomized 50 patients to either electrical stimulation or acupuncture alone, which was considered sham treatment. Patients on active therapy experienced profound reduction in lower-extremity pain (56% versus 14%), increased physical activity (48% versus 13%), and improved sleep quality (41% versus 13%) compared with the sham treatment. Ninety-two percent of patients preferred the active therapy, and a similar majority reported an improved sense of well-being and willingness to pay "extra" for PENS.

In theory, electrostimulation could produce analgesia by inducing the release of endogenous opioid-like chemicals, and these trials seem to support a role for electrotherapy. However, there are obvious weaknesses in the study designs and practical obstacles to clinical use. It is almost impossible to compare electrostimulation with a true sham or placebo therapy. In addition, PENS, for all its absence of reported adverse effects, remains relatively invasive. Further, both studies had very strict and extensive
exclusion criteria that would prohibit a large fraction of the diabetic population from participating. The results are generally considered preliminary and difficult to imitate and maintain in a clinical setting (Mendell et al 2003).

Transcutaneous electrotherapy and percutaneous electrical nerve stimulation are alternative therapies that have demonstrated efficacy and may represent a hope for patients with severe, refractory pain.

**Low level laser therapy:**

LASER is an acronym of light amplification by stimulated emission of radiation. The principles upon which all laser devices are based were developed in early 20th century by Planck & Einstein. Planck proposed quantal theory, The idea that radiation could be considered as discrete quantas or bundles of energy, building upon Planck’s concept of quantal energies, Einstein presented a paper in 1917 entitled ‘zur quantum theori der starhlung’ which outlined the key principles for the stimulated emission of photons.

However, it was some 55 years back in 1955 the dream of building such device to produce stimulated radiation was realized by a group at Columbia University and named it as Maser, since it worked under microwave wave lengths. Within Three Years Schalow & Townes (1958) Proposed the Development of What Was Originally Termed an ‘Optical Maser’ based Upon the Maser Used at Columbia University. Despite this it was Dr.Theodore Maiman at Hughes laboratories in Malibu who published in 1960 the first account of the production of laser radiation using a Ruby crystal .This first laser device produced pulsed LASER visible radiation at a fixed wavelength of 694 nm and thus appeared red.( Printice et al 1998)
The 1960s saw very rapid developments in laser technology, it was this period in which laser production sources were multiplied. Crystal lasers include the synthetic ruby (Aluminium oxide and chromium) neodymium, yttrium, Aluminium, Garnet (nd.yag) lasers among others. Gas lasers were produced in the year 1961, the gas lasers developed include the helium neon (He Ne) argon & carbon dioxide along with numerous others. Semiconductor or diode lasers were developed in 1962 after the production of gas (He Ne) lasers. The Galium Arsenide (Ga As) was the first diode laser developed. Other lasers include liquid (organic dyes) lasers and chemical lasers, of which chemical lasers were used in military purposes.

The effects of low power Lasers are subtle, primarily occurring at a cellular level. Various vitro and animal studies have attempted to elucidate the interaction of photons with the biological structures. Some of the physiological effects of Laser are wound healing, tensile strength, immunological responses, inflammation, scar tissue, pain, bone responses, nerve responses.

Lasers have proved their significance in physiotherapy interventions on various studies conducted on it for the past 3 decades. Nowadays laser plays a major role in physiotherapy departments for treating various ailments like non healing wounds, inflammatory tissue responses, neuropathic pain, scar tissue management, arthritis, sprains, strains etc,. Low level laser have gained popularity because it appear to have only positive effects. Currently lasers are recognized as non significant risk devices. Although many empirical and clinical findings show promising results, more controlled studies are essential to determine the types of lasers and dosages that are required to attain reproducible results.
Low-energy laser is capable of producing an energy density so low that any biologic alterations are the results of a direct irradiation effect, not thermal events. In this system, the temperature elevations in irradiated tissues are limited to less than 0.1°C–0.5°C (Yu et al. 2004). Unlike traditional high-powered surgical lasers (their energy output can be up to 100 W), such as carbon dioxide, ruby, and neodymium–yttrium–aluminum–garnet (Nd-YAG) lasers, low-energy lasers are compact, low cost devices with an output power measured in milliwatts (Walsh, et al. 1997). Recent studies demonstrated that low-energy lasers are potential therapeutic instruments for rheumatoid arthritis management (Goldman 1980), modulation of wound healing (Lynons et al. 1987), postherpetic neuralgia (Ohtasuka, 1992), and recovery of nerve injury (Khullar et al. 1995). The continuous wave helium–neon (He–Ne) laser (632.8 nm) has been employed most commonly for these clinical treatments. Recently, in vitro studies have shown that low-energy lasers induce biostimulatory effects on cultured cells. Low-energy lasers induced macrophages to release factors that stimulate fibroblast proliferation (Young et al., 1989). An increase in production of pro-collagen, collagen, basic fibroblast growth factors (bFGF) and proliferation of fibroblasts after exposure to low-energy laser irradiation were noticed (Abergel et al., 1987; Yu et al. 2004). He–Ne laser treatment stimulated interleukin-8 and interleukin-1α release from cultured keratinocytes and induced an increase in the rate of keratinocyte migration and proliferation.

LASER as a therapeutic modality in the field of physiotherapy has undergone various researches since early 1960’s and many therapeutically significant results have been obtained from LASER. The present study focuses on the Neuro regenerative effect of therapeutic low level LASER on diabetic neuropathy.
1.7. STATEMENT OF THE PROBLEM

Diabetic neuropathy affects large population in our country which needs to be addressed efficiently. Diabetic neuropathy produces various symptoms like pain, sensory loss, weakness etc., particularly lower limb is mostly affected which is primary for locomotion and for Activities of daily living, so this particular problem has to be addressed effectively and conservatively to provide relief to persons affected by this problem. It is also estimated that overall prevalence of neuropathy in South Indian type 2 diabetic subjects is 19.1% (Ashok et al 2002), and among urban (Chennai) south Indian Type 2 diabetic subjects, the prevalence of Diabetic Neuropathy is 26.1% (Pradeepa et al 2008).

Diabetic neuropathy is a worldwide problem which affects all the classes, management for this problem in field of medicine is only aimed to clear the symptom rather than the nerve pathology. Medicines like insulin supplements and nerve vitamin and mineral supplements are added to manage these problems. Researches are going all over the world to treat the diabetes and its complications effectively in the field of medicine. Management of Diabetic neuropathy with physiotherapy is very limited and extensive research has to be done to address this problem conservatively in a physiotherapy perspective.

Laser as a therapeutic modality since its invention has produced many clinically significant result. Laser is used worldwide in physiotherapy for many clinical conditions like pain, inflammation, tissue healing etc, and much research is being conducted on nerve regeneration properties of laser, with this correlations laser can be effectively studied in the management of diabetic neuropathy.
1.8. NEED FOR THE STUDY

The extensive review of literature reveals that there is paucity of studies on role of neuro regenerative effect of low level laser therapy in experimentally induced diabetic neuropathy. The scope of management is also very less for this particular complication, this urges to do a study on this problem with low level irradiation which is recognized worldwide for its tissue healing properties.

**Current Status both Internationally and Nationally**

**International status**

Developed countries with their modern setup “know how” progressing rapidly in exploring the possibilities of low level laser to supplement the medical management and facilitate early recovery.

**National status**

The wealth of knowledge that has been passed by our researchers regarding the use of low level laser therapy for diabetic neuropathy has to be collaborated with detailed well organized study. Such a scientific study will facilitate Indian researchers and clinicians to use this modality effectively to treat diabetic neuropathy.