1.1. Background

The World Health Organization (WHO) has described diabetes mellitus as “Metabolic disorder of multiple etiology characterized by chronic hyperglycemia with disturbances of carbohydrate, fat and protein metabolism resulting from defects in insulin secretion, insulin action or both. The effects of diabetes mellitus include long-term damage, dysfunction and failure of various organs” (1). Diabetes is a form of chronic illness usually requiring glycemic monitoring, self-management education and support to prevent acute complications and to reduce the risk of long-term complications (2, 3).

Diabetes was first described in Egyptian culture in 15th century as “too great emptying of urine”. Hindu physicians in the Ayurveda developed the first clinical test for diabetes. They observed that flies and ants were attracted to the sweet tasting urine of people afflicted with certain diseases. Indian physicians around the same time identified the disease and classified it as ‘madhumeha’ or honey urine as they observed that the urine would attract ants.

In diabetes long standing metabolic derangement is associated with functional and structural changes in many organs, particularly those of vascular system, which leads to clinical ‘complications’ of diabetes. These characteristics may affect eyes, kidneys and nervous system (1). Such pathophysiological complications in type 2 diabetes are affecting middle aged and younger population worldwide at a rapid rate, leading to increase in epidemiology of type 2 diabetes worldwide.
1.2. Epidemiology of type 2 diabetes in India and Worldwide

Population growth, ageing of populations, and urbanization with associated changes in lifestyle is likely to cause a worldwide increase of 50.7% in number of diabetics by the year 2030. It is expected that there is an overall increase of 50.7% in number of diabetics from 2011 to 2030, with an average annual growth of 2.7%, which is 1.7 times the annual growth of the total world adult population (2).

Gandhi et al found physical inactivity, age, obesity, family history to be the primary risk factors that have been identified as a major contributing factor to insulin resistance and relative secretory defect in the pancreas (4). Though there seems to be a recent shift in the age trends as type 2 diabetes no longer remains a disease of elderly. Gandhi et al reported that age groups 20-79 years are equally affected with type 2 diabetes (4).

The global prevalence for all age groups is expected to increase from 2.8% in 2000 to 4.4% in 2030 worldwide corresponding to an increase from 171 million to 366 million (4). Possible reasons for ‘diabetes epidemic’ could be population growth, longer survival, urbanization, low physical activity, obesity, excessive energy intake and other factors (5,6). In Denmark, the prevalence of diabetes among 60-year-old subjects increased from 7.8% in 1974 to 12.3% in 1996 among men and from 5.6 to 6.8% among women. In a Norwegian study based on surveys in 1984 and 1995 of all inhabitants over the age of 20, the diabetes prevalence increased from 2.9 to 3.2%, but only in men (4, 8). World health organization (WHO) estimates 60 % of the diabetic population will be from developing countries in Asia by 2025 (3). Prevalence trends shows that all the nations are afflicted with the epidemic of type 2 diabetes, in a follow-up study of 8 years, McBean et al found a sharp increase in the prevalence, incidence of diabetes among elderly population of all ethnic groups (7), Misra et al found an alarming increase in the
prevalence of obesity, dyslipidemia, diabetes mellitus, generalized and regional obesity in middle age north Indian females (30). Similar findings were reported by Ramachandran et al, they reported that there is a large pool of subjects with impaired glucose tolerance at a high risk of conversion to diabetes (31, 32).

These findings clearly signify that global epidemic of diabetes and its related complications are on a rise and immediate attention is required to foster medical care and services in the community in order to promote a healthier ways of living among the affected population.

1.3. Epidemiology of Diabetic Peripheral Neuropathy (DPN) in type 2 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 (3). Prevalence of type 2 diabetes progressively affects middle aged and younger population worldwide. Most of the diabetics will belong to developing countries with the age range of 40-60 years at a higher risk of developing complications in diabetes. The highest regional prevalence was reported for North America (10.2 %) followed by South Asia (6.7 %) (8). The changing lifestyle, decreased physical activity and dietary habits clearly signify that there is a shift in the global epidemiology of type 2 diabetes and its complications like neuropathy, retinopathy and nephropathy, myocardial infarction and stroke or even mortality (9,10,33). The most frequently occurring complication in type 2 diabetes has been diabetic peripheral neuropathy (DPN) or distal symmetrical polyneuropathy (DSP). DPN affects up to 50-70% of the population with diabetes (11). In a study of 400 patients with depression, anxiety, and sleep disturbances in type 2 diabetes, two-third of depressed patients and three-quarters of anxious patients had pain, but the most important finding was that 90% of sleep-deprived patients had experienced pain (12). Gore et al showed that with increasing pain
severity, there was a linear increase in Hospital Anxiety and Depression Scale pain and depression scores. The impact of depression complicated the diabetes management, increased the length of hospital stays, and almost doubled the yearly cost of diabetes management from US$7000 to $11,000 (13).

In type 2 diabetes DPN is one of the commonest causes of foot complications leading to pain, loss of sensation, foot ulcers and amputation leading to a reduced functional capacity of an individual (14). In a study to determine the prevalence of foot ulcers and the incidence of amputations in patients with type 2 diabetes Bruun C et al observed that after 19 years of diagnosis of type 2 diabetes, the incidence of amputations was still high in type 2 diabetes population (15).

It is clear that high glucose levels in the body change the metabolism of nerve cells. This can result from the loss or damage to the sensory nerve fibers (1). The first problem is loss of sensation for pain. This increases the likelihood of ulcers in the diabetic population. It accounts for frequent hospitalization than other complications of type 2 diabetes and is also the most common cause of non-traumatic amputations (11). In addition to this in daily living, population with diabetic peripheral neuropathy (DPN) encounters problems with balance while standing and walking, reduced work related capacity and pain in the legs reducing their overall functional capacity leading to poor quality of life.

1.4. Pathophysiology

Diabetic neuropathy encompasses a variety of forms whose impact ranges from discomfort to death. Hyperglycemia induces oxidative stress in diabetic neurons and results in activation of multiple biochemical pathways. These activated pathways are a major source of
damage and are potential therapeutic targets in diabetic neuropathy. Though therapies are available to alleviate the symptoms of diabetic neuropathy, few options are available to eliminate the root causes. High glucose impairs the mitochondrial electron transfer chain, leading to excess production of superoxide and hydrogen peroxide, two highly Reactive Oxygen Species (ROS) (1). Superoxide combines with nitric oxide to form peroxynitrite that attacks and disrupts proteins and lipids (1). Superoxide also attacks the iron sulfur center of several proteins leading to inhibition of key enzymes, including electron transfer chain and tricarboxylic acid cycle (1). Hydrogen peroxide reacts with free iron and produces hydroxyl radicals. Hydroxyl radicals attack lipids, forming lipid peroxides that are directly toxic and mediate significant cellular injury (1). In addition to superoxide, hydroxyl and peroxynitrite radicals, alkoxyl, peroxy, hydroperoxyl radicals and reactive nitrogen radicals such as nitrogen dioxide and nitroxide form, further damaging proteins, lipids and nucleic acids. Over time and unchecked, ROS produce protein, lipid and nucleic acid damage that impairs nerve function and result in peripheral and autonomic nervous system injury and the signs and symptoms of diabetic neuropathy (11,14).

1.5. Available pharmacological therapies in DPN

Glycemic control is the only currently known therapy to delay the development and progression of DPN. Once a patient has been diagnosed with DPN, treatment options focus on symptom control. Previously there had been many studies focusing on drug related prophylaxis for population suffering from DPN such as antidepressants, anticonvulsants, oral hypoglycemic agents but either they have a major side - effect or cannot be continued for long term trials for patients (16). Antidepressants are a common group of drugs used for neuropathic pain. Tricyclic Antidepressants (TCAs), Selective Serotonin Reuptake Inhibitors (SSRIs) and Selective Norepinephrine Reuptake Inhibitors (SNRIs) have been tested for off-label uses in pain.
management (17). Amitriptyline was the first and most frequently studied TCA to show a significant improvement in pain scores. Later, other TCAs, such as desipramine and nortriptyline proved to have beneficial effects, still the most common and least tolerated 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 (17).

Routine supplementation with antioxidants, such as vitamins E and C and carotene, is not advised because of lack of evidence on its efficacy and concern related to its long-term safety (18). Benefit from chromium supplementation in people with diabetes or obesity has also not been demonstrated which is a subject of further research and cannot be recommended on a long term basis in the diabetes population (18). A daily multivitamin supplementation may be appropriate, especially for those older adults with reduced energy intake.

1.6. Non-Pharmacological therapies in the management of DPN

On the contrary, we still need to explore the role of prescribed physical activity on diabetic peripheral neuropathy as a measure to control the progression of DPN in diabetes. This method or mode of treatment will be of ample importance as it will be a very cost-effective and efficacious method to control progression of DPN, thereby lowering the risk of amputation or any kind of disability caused by DPN, reducing the functional capacity of the affected population. Efficacy of moderate intensity aerobic exercises in type 2 diabetes has already been established (19-22). Known effects of aerobic exercises lead to glycemic control, shift towards healthier lifestyle and prevention or modulation of risk factors in cardiovascular disease. There is an increasing emphasis on accumulation of 150 minutes or more of moderate physical activity/
week due to the pooled data from various researches and moreover it has become increasingly clear that physical activity is a therapeutic tool in a variety of patients with, or at risk for diabetes and its related complications. Most obese, type 2 diabetic individuals exhibit decrease in blood glucose levels after mild-to-moderate exercises (23). The magnitude of decrease in blood glucose is related to the duration and intensity of physical activity (23). Blood glucose reduction during physical activity is attributed to attenuation of hepatic glucose production, whereas muscle glucose utilization increases normally (23). Reduced hepatic glucose production may activate a negative feedback mechanism to sustain insulin levels during exercise and elevate glucose levels before activity. Mild-to-moderate intensity exercise lowers blood glucose, and this effect is sustained into the post-exercise period (23). Thus, mild-to-moderate intensity exercise is recommended to facilitate glucose reductions in those with type 2 diabetes. Blood glucose response to moderate exercise in lean, type 2 diabetic individuals is highly variable (23) and is not as predictable as in obese individuals (23). On the contrary diet can also plays an important role in lifestyle modifications and 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 (24).

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 and they should also receive proper supervision and monitoring during training. Caution should be used in cases of advanced retinal and cardiovascular complications (20, 25-27).

On the contrary, yoga can also be a therapy of choice as current evidences suggest acute benefits of yoga in type 2 diabetes (28). 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. Though there still needs to be a long term trial determining the chronic benefits of yoga in type 2 diabetes (28).

Dietary modifications are among the primary therapy 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). Monitoring carbohydrate, whether by carbohydrate counting, exchanges, or experience-based estimation, remains a key strategy in achieving glycemic control. For individuals with diabetes, the use of glycemic index and glycemic load may also provide a modest additional benefit for glycemic control over that observed when total carbohydrate is considered alone (29).