Mounting evidences suggest that diabetic peripheral neuropathy is the most common complication of diabetes mellitus and which not only refers to a reduced quality of life but also causes disabilities which might have life threatening outcomes. Diabetic neuropathy (DN) refers to an array of clinical signs and symptoms characterized by dysfunction of peripheral nerves when other causes of peripheral nerve dysfunction have been excluded (37). Distal symmetrical polyneuropathy (DSP) or Diabetic peripheral neuropathy (DPN) is the commonest form of neuropathy accounting to as high as 75 % compared to other forms of neuropathies seen in diabetes mellitus (37).

Diabetic peripheral neuropathy (DPN), whose prevalence is as high as 75% (37) in the diabetic population, is considered to precipitate a complex mechanism due to poor glycemic control which leads to insensitive feet and hands, leading to not only a poor quality of life but also to immeasurable psychological and social stress on a family (13). Though many drug therapies are available for the management of diabetic peripheral neuropathy, but none of them have promising results and have added adverse effects on an individual (16,17,77). Moreover, its role in disruption of the normal progression of DPN as a life threatening complication of type 2 diabetes is still doubtful.

On the contrary moderate intensity (Heart rate reserve of 40-60% or rating of perceived exertion (RPE) -somewhat hard) aerobic exercise of 30 min duration per session for 8 weeks can play a vitally important role in the control of diabetic peripheral neuropathy. As know with DPN, the body has increased reliance on polyol-sorbitol pathway (anaerobic process). In the first step of the pathway, glucose is converted to sorbitol by aldose reductase enzyme (AR) which is then
oxidized to fructose by enzyme sorbitol dehydrogenase. This increased sorbitol concentration and activity of polyol pathway not only decreases nerve conduction velocity but has deleterious effect on Schwann cell due to increased intracellular sorbitol concentration, leading to decreased endoneural blood flow and chronic hypoxic state of the nerves (74, 87).

In the present study there are plausible reasons that may lead to change in the nerve functions. As with moderate intensity exercise in DPN, there is a shift from the anaerobic system to the aerobic system, the aerobic exercise of moderate intensity (defined by duration and intensity of exercise) leads to metabolic adaptations in the body. As body relies more on the glycolytic pathway after aerobic conditioning, the end products of glycolysis, that is pyruvate, now participates in mitochondrial respiration by serving as a substrate molecule for Krebs cycle (74, 87). In the state of euglycemia, achieved due to aerobic training there is a reduction in the activity of aldose reductase which in turn decreases the production of sorbitol in the body. With moderate intensity exercise the metabolic adaptations decrease the high intracellular glucose concentrations leading to decline in sorbitol production and thereby preventing a state of chronic hypoxia for the nerves.

The effect of moderate intensity aerobic exercise on each of the primary outcome measures will be discussed in the forthcoming paragraphs and the possible role of exercise in preventing the deleterious effect of DPN in type 2 diabetes mellitus will also be outlined in detail.
5.1. Effect of aerobic exercise on Nerve Conduction Velocities (NCV)

Nerve conduction studies (NCS) are considered to be pragmatic standards in the study of physiology of nerves and still remains the most accurate, sensitive and reliable measure in the study of peripheral nerve functions (53,54). Usually in clinical trials a combination of sensory and motor nerve conduction velocities are recommended (53) as DPN affects both sensory and motor nerve fibers and moreover it is very important to have a clear clinical picture of the severity of DPN before a therapy is initiated for the disease. NCS shows the lowest degree of variance of all the measures in the study of neuropathy, hence it is considered the reference standard for the study of peripheral nerves in neuropathy (variance accounting to 5-10% only) (53).

5.1a. Peroneal motor nerve conduction: Early work of Buchthal and Rosenfalck showed that conduction velocities are more reproducible than amplitude (53). Nerve conduction velocities have long been used as a surrogate marker to indicate the outcome of a therapy for patients with peripheral neuropathy.

A study determining the role of motor nerve conduction velocities to predict foot problems like amputation, foot ulcers and mortality over a period of 6 years showed that Motor Nerve Conduction Velocity (MNCV) can predict new ulcerations and deaths in type 2 diabetes (96). In the present study there were novel findings, in the control group where the patients were on standard care, we found a decline in the mean conduction velocity of peroneal nerve by -0.192 meter/second (m/s) whereas at the same time in the study group there was an increase in the mean conduction velocity by 3.08 m/s over a period of 2 months of intervention with moderate intensity exercise and standard care which was significantly different for two groups (p < 0.05).
Another study by *Dahl-Jorgensen* which followed the patients over a period of 8 years compared the effect of intensive glucose control (study group receiving multiple injections of insulin therapy/day) with standard control (one or two insulin injections/day) and found a mean increase in peroneal conduction velocity of the study group (72). The authors reported a small but significant mean annual change in peroneal motor nerve conduction velocity of the study group by 0.61 m/sec as compared to the standard care group or the control group (standard care group) there was an annual decline in mean velocity of peroneal motor nerve by -0.33 m/sec. Furthermore it is relatively known that the decreased conduction velocity of sensory and motor nerves is relatively specific for a decreased number of large myelinated peripheral axons.

A study by *Shichiri et al* (2000) studied 110 participants for eight years with type 2 diabetes comparing the conventional therapy or standard care (one or two insulin injections/day) with intensive therapy group or the study group (three or more insulin injections/day) for the onset and progression of the early stages of diabetic microvascular complications, found an increase of 0.44 m/s in the conduction velocity of the median nerve (sensory and motor) of the intensive therapy group and found a decline of 0.13 m/s in the conduction velocity of the conventional therapy group (88). In conclusion the author reported a small but a significant difference for conduction velocity of the patients treated with intensive therapy group.

Though studies have included ulnar nerve, median nerve and radial nerve as a measure for neuropathy in the clinical trials, still very important question regarding the clinical manifestations of DPN still needs to be addressed, that is, though the upper-lower limb nerves are symmetrically affected but the severity of lower limb nerves getting involved in DPN is higher because of its ‘fiber length-dependent’ relationship (53). Hence chances of finding changes in the peripheral nerves of the lower limb
are higher and should be considered as lower limb nerves will be more sensitive to the changes in type 2 diabetes than the nerves upper-limb alone.

A Cochrane based review in 2012 which compared the effect of intensive glucose control (study group), (three or more insulin injections/day) with conventional glucose control (standard care group, one or two insulin injections/day) in type 2 diabetes population found that intensive glucose control group had no added benefit over conventional form of therapy (72). Moreover they found studies reporting a higher number of incidence for neuropathy in type 2 diabetes as compared to type 1 diabetes.

The Action to Control Cardiovascular Risk in Diabetes (ACCORD) trial investigated the effects of intensive versus standard glycemic control therapy for hyperglycemia on risks of cardiovascular events in a large population with type 2 diabetes demonstrated a 0.70% per year risk reduction (non-significant) at a median of 3.7 years of follow-up in those receiving intensive therapy. The study further reported adverse events for intensive therapy groups, like risks of hypoglycemia were 3 times higher in the intensive therapy group or enhanced glucose control group. Weight gain and number of deaths were reportedly higher in the intensive therapy group than conventional forms of treatment (89, 90).

**5.1b. Sural sensory conduction:** Sural sensory nerve is sensitive to changes induced by hyperglycemia in the body and is affected early in diabetes (51). It was observed by Eaton et al. That endoneural blood flow is usually impaired in the early stage of diabetes leading to small and large fiber dysfunction in the lower limbs (91). Sensory nerve conduction studies always add to the clinical picture of neuropathy provided by motor nerve. Furthermore, decreased conduction velocity of sensory and motor nerves is relatively specific for a decreased number of large myelinated peripheral axons or for decreased myelination of these fibers (53). It is reported that even if the amplitude of sensory nerve action potentials is normal the amplitude of the motor nerve may be affected usually due to loss of nerve
fiber from the nerve root level or anterior horn cells in the spinal cord, hence to have a clear finding for a clinical trial usually it is recommended that both sensory and motor components of NCV should be undertaken (53). Moreover, nerve conduction studies are less variable and therefore it is more suited for monitoring diabetic neuropathy (51).

In the present study we found that there was a gain of 0.301 m/s (mean difference) with standard care in the control group whereas in study group with exercise and standard care there was a gain of 7.729 m/s (mean difference) which was significantly different for two groups (p < 0.05). The small gain in sural nerve conduction velocity that we observed in the control group could also have been due to insulin dosage which increased at the end of the study for the control group (n=7) (mean increase of 3.242 units). Whereas, there was a mean decrease (1.644 units) in dosage of insulin with exercise at the end of 8th week in the study group (n=4).

In a study where patients were followed up with the aim to investigate the association between human insulin and cancer incidence and mortality in Chinese population with type 2 diabetes, the investigators found higher risks of liver cancer and higher risks of overall mortality rate from cancer to be significantly higher among the insulin users than the non-insulin users (92). Though the results were alarming, as the results of the study suggests precaution in the use of intensive insulin regime in the management of type 2 diabetes, still interpretation of the results of the mentioned study requires caution as the study had a few limitations, firstly it was a non-randomized trial and secondly discrepancies were present at the baseline in the characteristics of two cohorts.

A higher dosage of insulin therapy comprising of multiple injections a day (≥ 3 injections/day) which is initiated with the goal of attaining good glycemic control in type 2 diabetes may have added
hazardous effects (72, 93) and benefits of glycemic control can be outweighed against the risk of severe hypoglycemia and higher rates of mortality as it is evident from previous studies (72, 93).

In the present study exercise had an ameliorating effect on drug dosage (table 13) which usually play a vital role if considered early in the management of type 2 diabetes. Moreover, previous researches have already established the merits of moderate intensity aerobic exercise in lowering insulin resistance, glycemic control and improving vascular functions in type 2 diabetes (19). Exercises also leads to lower dependence on antidiabetic drug regime and helps in modulation of an individual towards healthier lifestyle (19). Whereas there is dearth in literature on the long term efficacy of antidiabetic drugs as a recent study with a 5 year follow-up on the efficacy of metformin, sulfonylureas and insulin by Bowker et al found that there was an increase in mortality related outcome in sulfonylurea and insulin group as compared to metformin group alone (94).

On the contrary, the results from earlier researches have proved that moderate intensity exercise can delay the onset of neuropathy and can also have added benefits of physical and psychological attributes of an individual. Therefore with the results of the present study we strongly recommend that structured aerobic exercise training can alter the natural progression of DPN. Hence from the present findings it can be substantiated as a valuable line of management along with the current or existing form of therapies in the treatment of DPN.

Exercise not only helps to modulate metabolic control (HbA1c), but also improves insulin sensitivity and antioxidant system in type 2 diabetes (19). In DPN however, there can be various plausible mechanism by which aerobic exercises helps to modulate the progression of neuropathy. Firstly, with moderate intensity aerobic training there is a shift from polyol-sorbitol pathway to the glycolytic pathway leading to modulation of neuropathy. This shift to aerobic pathways is characterized by metabolic
adaptation of the aerobic system of the body which leads to decrease in formation of aldose reductase due to reliance on aerobic system. This decrease in aldose reductase flux may increase the generation of nitric oxide in endothelial cells, thereby causing decreased production of sorbitol in the body that has a deleterious effect on peripheral nerves (sural and peroneal). Secondly, with aerobic exercise training there is an increase in the tissue antioxidant capacity of the body. As due to increase in oxidative stress because of hyperglycemia in type 2 diabetes (87, 95), there is damage to the peripheral nerves in the body. By maintaining the state of euglycemia in the body by means of aerobic exercise, we decrease this state of oxidative stress on the body systems.

Even Eurodiab study (2010), concluded that microvascular disease complications have strong correlation with that of low conduction velocity and amplitudes of the peripheral nerves in type 1 diabetes (96). Hence from this study, we observe the added benefits of moderate intensity exercise as an objective hallmark in disrupting the normal progression of neuropathy without any adverse events in patients suffering from diabetic neuropathy.

5.2. Neuropathy quality of life (NQOL) questionnaire

There are various factors in type 2 diabetes that may deteriorate the quality of life of patients with peripheral neuropathy. In patients with type 2 diabetes, DPN may involve small fiber dysfunctions leading to painful legs or it may progress with large fiber dysfunctions causing loss of protective sensations leading to foot ulcers and amputations. Although only 11% of the population suffer from painful neuropathy but its prevalence greatly reduces the quality of life (QOL), sleep and can lead to depression in diabetic patients (97).

Neuropathy Quality of Life that we used in the present study had following components consisting of pain, lost/reduced feeling in feet, sensory-motor symptoms, restricted activity of daily living (ADL),
Discussion

disruptions in social relationships, emotional distress, specific impact on QOL, overall quality of life, total score. NQOL measures individual’s health function, health perception and health status in relation with specific issues pertaining to diabetic foot. It measures the interference caused by problems associated with diabetic foot in social, emotional and day to day activity level. An increase in the total score is reflected as deteriorating QOL in DPN. In the present study we found an increase in the scores for overall impact on quality of life indicating deterioration of QOL in the control group, whereas the scores in the study group decreased implying an improvement in QOL (table 2).

Psychological benefits of exercise in type 2 diabetes are well known (98-100). A Systematic review and meta-analysis of randomized controlled trials outlined that in type 2 diabetes, there can be improvements in psychological distress but not in weight control or blood glucose concentration in people who receive psychological therapies (89). In the study group we found a significant reduction in the scores for the components of NQOL (p < 0.05). The difference in the total scores was significant (p < 0.05) for the control and the study group of NQOL. This is the first study measuring the effect of moderate intensity exercise on quality of life of DPN patients in type 2 diabetes mellitus. The merits of moderate intensity exercise can be evaluated from the fact that it resulted in improved quality of life, which could also be postulated to be due to the effect of moderate intensity aerobic exercise that enhance the glycemic control of the body resulting in reduction in HbA1c levels (table 16). The study group reported a mean reduction of 0.79% from baseline for metabolic control (HbA1c) as the study group had an enhanced glucose control due to the effect of moderate intensity exercise.

Lesser scores for sensory-motor symptoms, restricted activity of daily living (ADL), disruptions in social relationships, specific impact on QOL in the study group, indicates that moderate intensity aerobic exercise helps in modulating health behaviors in type 2 diabetic population. Emphatic effects of exercise
on psychometrics and physical measures have been reported previously in type 2 diabetes (89, 98). As with lifestyle interventions, patient commitment to exercise training in type 2 diabetes is preceded by counselling and adherence to the exercise training regimes to move forward in the training regime through preparation, action, and maintenance of behavioral change. It is quite evident from behavioral research in type 2 diabetes that a variety of factors contribute to the adoption of healthy exercise patterns, including perceived barriers and benefits, self-efficacy, motivation, social support, access, and provider’s support, as well as modulation of anxiety and depression (98,101-105). Hence in the present study supervised aerobic exercise with standard care appears to be superior to other forms of treatment as it not only improved the metabolic and objective measures of DPN, but also resulted in the change of NQOL scores of patients in the study group. However, in the control group, standard care alone did not result in enhancement of neuropathy quality of life, as modulation for healthy lifestyle could not occur in due time with standard care.

Quality of life in clinical trials is usually considered to be a distinguished feature of a trial in defining outcome to a therapy. Aim of any therapy in type 2 diabetes is to enhance glycemic control or support health behaviors or activities that lead to modulation in their health related quality of life.

It is very important to understand the effect of intensive glycemic control on QOL which still remains to be defined, as there is lack of evidence supporting the fact that intensive drug or insulin therapy results in improvement of QOL. ACCORD 2010, shares the fact that intensive glycemic control of HbA1c < 6 % places a lot of the burden of self-management on the patients, moreover adverse effect of intensive therapy cannot be ignored that places patients at lot of risks of severe hypoglycemia requiring hospitalization and increasing their fear for hypoglycemia. Even long term follow up in ACCORD study group with intensive glycemic control did not lead to improvement in QOL in patients.
Discussion

with type 2 diabetes (106). Finally the trial had to be discontinued due to increase in the death rates of the intensive therapy group (> 3 insulin injections/day) (93).

A decline in pain, sensory-motor symptoms scores of NQOL was observed in the study group which had a significant difference by the end of the study duration (table 21). The mechanism behind this might be the same as we have mentioned above that moderate intensity exercise leads to metabolic adaptations that in turn causes decrease in formation and deposition of sorbitol in the parenchyma of the nerves. This is the first study signifying the role of moderate intensity exercise on pain and sensory-motor symptoms. Exercise could be a cost-effective measure compared to the drugs available for the treatment of painful neuropathy.

On the contrary, whether the drug therapy might be of use in the treatment of painful symptoms in DPN is unclear, as a Cochrane based review evaluating the possible benefits and harms of duloxetine in the management of neuropathic pain associated with diabetic peripheral neuropathy concluded that at the dose of 60 mg/day, there was evidence that duloxetine reduced pain in painful diabetic peripheral neuropathy. But most people taking duloxetine reported at least one side effect. These were feeling sick, being too awake or too sleepy, developing a headache, having a dry mouth or becoming constipated or dizzy. Though duloxetine is the most efficacious drug in the management of painful neuropathy but still about one in six people is usually reported to stop duloxetine because of its side effects (107). Another Cochrane based review by Moore et al assessing the analgesic efficacy and associated adverse events of pregabalin in acute and chronic pain in peripheral neuropathy concluded that only a minority of patient population with these types of pain will have a substantial benefit. They further added that with dosage as high as 600 mg, pregabalin patients reported daily somnolence of 15% to 25% and dizziness occurred in
another 27% to 46%. Treatment was discontinued as 18 to 28% of patients had adverse reactions to the drug (108).

The prevalence of depression in diabetes is common and may be even responsible for poor glycemic control, which may be due to non-adherences to physical activity. A study examining the possible role of physical activity in older adults (99) found that decrease in physical activity negatively impacts the health related QOL in diabetes. Moreover, it has been documented that lower level of physical activity is associated with poor health related QOL and is independent indicator of increased cardiovascular related mortality risks in type 2 diabetes (68). Even low threshold of physical activity is appreciable in type 2 diabetes and can help to modulate or reduce risk factors in type 2 diabetes. Even low intensity exercises like home based brisk walking is also reported to induce a better metabolic control and can be advised for the patient population, as it might help in improving the health related QOL in DPN (109).

A Dutch study examining the patient characteristics associated with quality of life found that insulin therapy, obesity and complications of type 2 diabetes were associated with a lower levels of health related QOL (110). Hence there appears a need for designing an intervention that can not only minimize complications in DPN but also results in increased levels of overall health related perception, decrease in depression and have fewer adverse effects. It is well understood from the present evidences that exercise is beneficial and should be implemented for the patient population with poor metabolic control suffering from depression and poor health related NQOL in type 2 diabetes.
5.3. Metabolic control in type 2 diabetes

Benefits of exercise on glycemic control are enormous. Moderate intensity exercise with medium to high volume of exercise leads to desired effect on controlling the blood sugar levels in the body (105). If we quantify the effect of moderate intensity exercise, it appears to be a modest one causing an average reduction of 0.8 % in HbA1c (19,112,113). However small these changes might appear, they can still significantly reduce the chances to develop microvascular or macrovascular complications. Moreover these changes induced by exercise alone are equivalent to changes induced by intensive drug therapy (114) with no added burden of adverse effects as induced by intensive therapy. Exercise also results in lower dependence on antidiabetic drugs due to increase in insulin sensitivity of the body (115,116).

HbA1c is a gold standard for glycemic control in diabetes as it accurately reflects glycemic control over a period of time (117). It also predicts hyperglycaemia related complications in due course of time for patients suffering from type 2 diabetes mellitus. Hence any effort to lower HbA1c levels usually results in delaying microvascular related complications in type 2 diabetes mellitus (118,119).

In a clinical setting, type 2 diabetes usually presents with poor glycemic control which increases the morbidity and mortality risk in the population. High HbA1c concentrations are not only associated with an increased risk of developing DPN but it may also impose risks of developing diabetic retinopathy and nephropathy in due course of time (111,120-122).

In the present study, aerobic exercise with standard care had an antiglycation effect which resulted in a mean reduction of glycosylated hemoglobin levels in the study group by 0.79 % and this difference on analysis was significant (p < 0.05). Whereas, the control group showed a mean increase of 0.01 % in the mean glycosylated levels from baseline. This clearly signifies the empirical foundation laid by exercise in
the metabolic control of type 2 diabetes which ameliorates the progression of micro and macro vascular complications.

United Kingdom Prospective Diabetes Study (UKPDS)-35 a prospective observational study which aimed at finding an association of glycaemia with macrovascular and microvascular complications in type 2 diabetes, demonstrated a 14 % reduction in the incidence of acute myocardial infarctions, 21 % reduction in diabetes related deaths, with every 1 % reduction in the HbA1c levels in type 2 diabetes mellitus (111). Whereas UKPDS-33 study group, comparing intensive blood-glucose control of sulphonylureas or insulin with conventional form of therapy (or standard care) for risk of complications in patients with type 2 diabetes found a 10 % lower incidence of diabetes related deaths from myocardial infarction, stroke, peripheral arterial disease and sudden death, with every 1 % reduction in HbA1c levels in patients with diabetes mellitus (114).

European Prospective Investigation into Cancer (EPIC)-Norfolk study estimated 12 % deaths in type 2 diabetes can be prevented if we lower the mean glycosylated hemoglobin of the population by 0.1 % and a 25 % reduction in the number of deaths could be expected by lowering the mean HbA1c of the population by 0.2 % (123). Furthermore increase in HbA1c is also associated with risks of lower extremity amputation in type 2 diabetes. With every 1% increase in HbA1c levels there is a substantial increase in risk of lower extremity amputation (124). Another prospective study of 10 years duration found that peripheral neuropathy is an independent indicator of lower extremity amputation in type 2 diabetes (125). Hence we can postulate from the findings of the present study about the beneficial effect of moderate intensity exercises in DPN that not only improves objective and subjective measures of DPN but can also lead to an overall reduction in risk of amputations and deaths in type 2 diabetes by modulating risk factors which may compromise a patient’s life due to progression of neuropathy.
Height and age appear to be unmodifiable risk factors in the development of neuropathy in type 2 diabetes (11,139). Despite of the increased duration of the other risk factors in the study group (table 10), moderate intensity aerobic exercise helped in modulating these risks factors by means of aerobic conditioning of the body, which further prevented the deleterious progression of neuropathy. Our understanding in the present study becomes clearer, regarding the vitally important line of therapy portrayed by moderate intensity exercise in the management of DPN. From the present study it is postulated that exercise have a neuro-protective effect on the peripheral nerves of the lower limb as it was observed by an increase in mean value of conduction velocity of the study group (table 18, 20).

Weight gain remains an important risk factor in type 2 diabetes. A review analyzing the effect of interventions like physical activity and diet on overweight and obese individuals using trans-theoretical model found that a combination of physical activity and diet resulted in minimal weight loss, and there was no conclusive evidence for sustainable weight loss. They further stated that trials even reported that there was a significant weight gain for both intervention and control groups after 12 months of duration of the study (126). In the present study we also did not find any significant difference between the two groups for changes in weight or anthropometric measures in the study group by the end of 8 weeks. This could be attributed to a greater duration of risk factors (table 10) and secondly modulation in weight with exercise may require more than 8 weeks to produce any significant changes.

A retrospective study by Currie et al concluded that optimum glycemic control required, should be restricted to HbA1c levels 7.5 % in type 2 diabetes as they found value of 7.5 % was associated with lower mortality rates (119). They also found that an increase or decrease from this value had a greater susceptibility of cardiac events or mortality. In the present study we also found that with exercise the mean value of HbA1c reduced from 8.37 (1.92) to 7.58 (1.4). It was observed that similar changes were
also seen in sural and peroneal nerves after moderate intensity exercises. We can also hypothesize here that optimum changes that occurred in objective measures of neuropathy in the intervention group could also have been because we attained the optimal range of HbA1c with exercise, similar findings for optimal range of HbA1c were also reported by Currie et al (119). They further reported HbA1c as an independent marker for mortality and adverse event in diabetes.

Insulin is usually used to achieve better glycemic control in patients with type 2 diabetes frequency and dosage of insulin usage can also act as a surrogate indicator for complications in type 2 diabetes and all-cause mortality (127). Moreover with intensive therapy (multiple injections of insulin) there is an increased chance for hyperglycaemia and hypoglycaemia related fear, limiting the ability of current diabetes medications to achieve and maintain optimal levels of glycemic control (93,111,123,132). On the contrary exercises used to maintain glycemic control carries lower risks for hypoglycemia (19). More prudent use of exercise with standard care as a therapy may lower the risk of hypoglycemia, may also help patients achieve improved glucose control for longer period of time, and thus reduce the risk of complications in type 2 diabetes.

Position stand of the American Diabetes Association (ADA), defines optimal ranges to be achieved for patients with diabetes for HbA1c levels ranging from 5 - 6.5 or lowering HbA1c to below or around 7% have shown to reduce microvascular and neuropathic complications of type 1 and type 2 diabetes, still the current evidences suggest a variability from the aforementioned position stand which is a subject of further research. For microvascular disease prevention, the HbA1c goal for non-pregnant adults in general is < 6.5 % (128). ACCORD reported a higher mortality rates with intensive glycemic control (HbA1c < 6%) (> 3 Insulin injections/day) than the conventional or standard care group (< 3 Insulin injections/day) (93). As there is disparity in position stands laid by ADA and current evidences regarding
the optimum limits of control in HbA1c, future trials should be designed determining the safe limits of glycemic control for the patient population in type 2 diabetes. Hence for now if we carefully weigh the available evidences, we should consider the optimum ranges for HbA1c for glycemic control as 7-7.5% as proved by the researches (119).

The overall implication of the research is that exercise is an important core of non-pharmacological management in type 2 diabetes. It not only helps to minimize other cardiovascular complications in type 2 diabetes but also helps to improve peripheral nerve functions thereby halting the normal progression of DPN.

5.4. Correlation findings in the study for various outcome measures

There were few novel correlations that we observed in the present study. We found a weak to moderate Pearson correlations for various variables in the study that have been discussed in this section which will help us to broaden our insight for research in DPN.

There are evidences that suggest a strong association of higher BMI with poorer self-perception and health related QOL and among the diabetic complications, the history of a stroke and neuropathy are the strongest predictors of reduced health scores (129). Moreover, a systematic review of RCT of psychological trials found improvement in psychological distress but no improvement in weight control of the individuals even with various psychological therapies (89), similar findings were reported with interventions like diet and physical activity on weight loss in overweight and obese adults (126). It is known since long that there is an association between duration of diabetes and metabolic risk factors like BMI, WHR, waist circumference and usage of insulin and medications. A number of studies have identified BMI and WHR (111,130,131) to predict risks for mortality and morbidity which further gets amplified with duration of diabetes. We found a weak correlation between duration of diabetes and BMI
(−0.252) and duration of diabetes and WHR (0.263). MDNS scores also showed moderate correlation (0.347) with duration of diabetes a simple reason could be with increase in duration of diabetes peripheral sensation gets compromised.

In our study we found a moderate positive correlation (0.434) between duration of diabetes and dosage of alpha glucosides inhibitors in DPN population. As a therapy for glycemic control the role of alpha-glucosides inhibitors is doubtful (133) as in a review, Krentz et al found that alpha-glucosides inhibitors were less effective for glycemic control. On the contrary they found metformin of biguanides group to be more effective in controlling weight gain with added beneficial effect on various cardiovascular risk factors (133). They further recommended that pharmacological treatment to be individually tailored and dosage to be titrated according to the glycemic control.

The Constitution of the World Health Organization (WHO) defines health as “A state of complete physical, mental, and social well-being not merely the absence of disease”. They have further stated that “measurement of health and the effects of health care must include not only an indication of changes in the frequency and severity of diseases but also an estimation of well-being and this can be assessed by measuring the improvement in the quality of life related to health care”(66). Usually higher scores for all the components of NQOL signify greater neuropathy related disability. We found glycemic control (FBS and PPBS) had a moderate correlation with NQOL ($r = 0.326$, $r = 0.385$). The novel finding in the present study was that we found a moderate correlation of HbA1c with that of NQOL which implies that glycemic control has a relationship with Neuropathy related quality of life in type 2 diabetes.

A moderate correlation of NQOL with NCV was also reported which is the most absolute finding in the present study. Peroneal nerve (peripheral segment) and sural nerve had a moderate negative correlation of $r = -0.329$ and $r = -0.343$ respectively. It is already well documented that diabetes is
associated with depression, mood variation and changes in health attitudes (67-69). In this study we also found relationship of psychometric and physical properties with NCV which is considered the pragmatic reference standard in the evaluation of neuropathy. Though in the present study we didn’t find any significant change in anthropometric measures across two groups but still with moderate intensity exercise there was improvement of psychometric and physiological measures. Hence it is of utmost importance to understand that health perception can be improved even without clinically significant change in anthropometric measures. On the contrary standard care group didn’t have any improvement in NQOL or physiological measures.

Decrease in physical activity has also been recognized to be associated with reduced nerve functions in type 2 adults (122,123) and its role in the management of type 2 diabetes is an essential part similarly pharmacological management has an important role in the management of type 2 diabetes and its complications. A study examining the relationship between reduced physical function in type 2 adult and peripheral nerves found that reduced peripheral nerve functions were associated with lower scores for physical performance (134). Though this study did not analyze QOL but it is clear from the present study that physical activity plays a vitally important role in preserving peripheral nerve functions and also helps to modulate health behaviors. There are studies that suggest that physical exercises not only promote psychological well-being but also supports physiological changes in the peripheral and central nervous system of the body. In a study by Gondoh et al aerobic exercise was reported to be associated with psychological well-being and inhibition of volume loss from gray matter in insula of the brain (100).

In the present study we found a moderate negative correlation of MDNS with peroneal nerve (-0.478), tibial (-0.374) and sural nerve (-0.494) velocity. Present study findings are in agreement with the study conducted by Feldman et al who also reported a moderate correlation of the MDNS with NCV.
(60). Application of the clinical component of MDNS should be a useful tool in everyday practice to confirm the presence of neuropathy and allow stratification of risk in the population. Moreover clinically it is important to approach neuropathy with stratification of risks factors and the staging associated with it (46). There are various scores like Valk score, Neuropathy disability scores (NDS), Michigan Diabetic neuropathy score (MDNS), which can be used for clinical stratification and can be used for staging neuropathy into mild, moderate and severe forms. These scores can be an excellent tool to measure prognosis of neuropathy to any therapy. MDNS has moderate correlation with nerve conduction velocity and can be a useful tool to measure prognosis to any therapy. More detailed staging of neuropathy, in particular to monitor its progression or response to treatment, requires that the patient undergo routine nerve conduction studies. Although performing NCV requires expertise and procedure is cumbersome to perform in a clinical scenario. However, as these diagnostic criteria are both time consuming and expensive, we believe that the MDNS (clinical scales) may play an important role in the diagnosis, staging and prognosis of DPN in response to disease modifying therapy.

5.5. Reversibility of peripheral nerve functions

The phenomenon of reversibility of diabetic peripheral neuropathy still remains to be established through clinical evidences. This is the first study of its kind in diabetic peripheral neuropathy outlining the effect of moderate intensity exercises on the normal course of diabetic peripheral neuropathy. We observed that moderate intensity aerobic exercise resulted in metabolic control, restoring the clinical abnormalities (NCV) induced by long standing poor glycemic control in type 2 diabetes. Exercise had an evanescent effect on sensory symptoms of pain and paresthesia. This was possibly due to reversal of impaired oxygenation of peripheral nerves. In the study group at baseline there were 46.2 % of patients with mild staging of neuropathy and 53.8 % of patients with moderate staging of neuropathy. Post
therapy there were 25.6% patients with mild staging of neuropathy and 14.8% of patients with moderate staging of neuropathy, whereas there were 35.9% of patients with no neuropathy staging. In the control group at baseline there were 37.5% of patients with mild staging of neuropathy and 62.5% with moderate staging of neuropathy. By the end of study duration, there were 22.9% of patients with mild staging and 57% of patients with moderate staging of neuropathy, only 2.1% patients had no neuropathy staging. This reversibility in clinical neuropathy represented by staging on MDNS occurred due to physiological adaptations to aerobic training in the study group where a higher percentage of people (35.9%) had a no neuropathy staging compared to control group (2.1%) where patients were only on standard care.

Recent empirical researches on strict glycemic control by intensive therapy (≥ 3 insulin injections) remains the pragmatic reference standards to control the progression of DPN. But before bringing these facts into practice we should weigh the risk on increased mortality and risks of hypoglycemia associated with it long term use (93). On the contrary to this practice if we combine standard care (≤ 3 insulin injections) with physical activity it will results in more benefits than standard care alone or starting intensive therapy for attaining glycemic control in type 2 diabetes population.

At present there is a need to search for newer therapeutic paradigm in the management of diabetic peripheral neuropathy. Still we haven’t exploited moderate intensity aerobic exercise to understand the mechanism by which exercise can maintain a state of euglycemia in the body and can also halt the process of neuropathy which is progressive in nature.

By the present study we can reach a conclusion that moderate intensity exercise (Heart rate reserve (HRR) 40-60 %) remains a hallmark in the management of DPN and its related complications. Exercise can be an excellent tool to ameliorate neuropathy from moderate to mild and no neuropathy stage. This
principle of reversibility of segmental nerves is observed more in mild than moderate forms of neuropathy. A reason for restoration of peripheral nerve functions could be inhibition of aldose reductase (AR) caused by aerobic exercise which leads to sparing of NADPH (Nicotinamide Adenine Dinucleotide Phosphate hydroxide) which then participates in the synthesis of nitric oxide thereby relieving the nerves from their hypoxic state (figure 14).

We should understand that there is a ‘no point of return’ in neuropathy that strongly depends on the duration of diabetes. Chances for neuropathy to have maximal reversibility (70-100% recovery in nerve functions) with aerobic exercise is higher in individuals with duration < 10 years, moderate reversibility (50-69%) seen in duration 10-20 years, slower reversibility (20-30%) seen in duration > 25 years and with duration greater than 25 years we reach a point of no return (137).

Hence the bottom line is, earlier we start with the moderate intensity aerobic exercises in peripheral neuropathy greater are the chances to observe reversibility in both signs and symptoms of neuropathy in type 2 diabetes, thereby preventing further progression of DPN to a life threatening complications.