3.1. Ethical approval: Ethical approval of the study was obtained from the university ethical committee in 2009 before the commencement of the study (Ethical clearance number: UEC/54/2009) (appendix). Patients were recruited from the hospital outpatient clinic; they were then explained about the procedure of the study. A written informed consent was obtained from all the patients before their participation in the study.


3.3. Study center: Kasturba Hospital, Manipal and TMA Pai hospital, Udupi, Karnataka.

3.4. Study duration: September 2009 to December 2012.

3.5. Study subjects: Patients in the study consisted of age group 30-69 years with diagnosis of type 2 diabetes and having clinical signs of diabetic peripheral neuropathy.

3.6a. Inclusion criteria:

- Patients were included if they had clinical neuropathy which was defined as a minimum score of 7 in Michigan Diabetic Neuropathy Score (MDNS).
- Age group of 30-69 years with diagnosis of type 2 diabetes having clinical signs of diabetic peripheral neuropathy.

3.6b. Exclusion criteria:

- Before beginning the exercise program, all the patients with type 2 diabetes mellitus underwent a detailed medical evaluation with appropriate diagnostic studies. These examination screened the participants for the presence of macro- and microvascular complications that may be worsened by the exercise program (proliferative retinopathy or nephropathy, including microalbuminuria).
• Other causes of peripheral neuropathy ruled out on subjective or objective clinical examination and on relevant laboratory investigations,

• Postural hypotension, foot ulcers, walking with assistive devices, part or complete foot amputation, peripheral arterial disease,

• Vision impairments or recent history of active retinal hemorrhage or if there had been a recent therapy (less than six months) for retinopathy,

• Neurological or musculoskeletal impairments, acute sciatica or vestibular dysfunction, cognitive impairments (n=7),

• A score of 30 or greater on MDNS, known at cardiac risks through clinical examination or diagnostic tests (coronary heart disease with abnormal electrocardiography stress tests),

• Abnormal electrocardiography at rest, recent revascularization of coronary artery bypass grafting (less than three months), and age greater 70 years.

3.7. Sample size calculation

The sample size was calculated based on the standard deviation between the mean of 2 observations of the sample of peroneal motor nerve (primary outcome measure) in the population with type 2 diabetes.

\[ N = 2[(Z \alpha + Z \beta) s/d] ^2 \]

= 36 in each group

N =72; N=86 (Including 20% drop outs), power of the study was 80%
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Where,

\[ Z_\alpha = 1.96 \text{ (at 95\% confidence interval)} \]

\[ Z_\beta = 0.87 \text{ (Power = 80 \%)} \]

\[ s = \text{Standard deviation between 2 mean observation of samples of peroneal motor nerve was taken to be 3 from the previous study (138).} \]

\[ d = \text{Estimated smallest difference of 2 was considered clinically significant for the study.} \]

3.8. Study design

3.8a. Setting and Randomization: Patients with the diagnosis of diabetic peripheral neuropathy from the hospital outpatient department were screened for inclusion/exclusion criteria before there enrollment in the study. This was a parallel group randomized controlled trial (RCT), conducted in Kasturba medical hospital, Manipal, Karnataka, India. Block randomization was used in the trial design to reduce the bias and achieve a balance in the allocation of participants to study and control arms. The randomizations of patients to the study group (n=42) and control groups (n=45) were performed using computer generated random number table.

342 patients were screened out of which 335 met the criteria for diabetic peripheral neuropathy. Only 87 patients gave their final consent to participate in the study. In each stratum there were total numbers of 5 Blocks with size of 10. At the end of the study there were 8 dropouts (18\%) in the control arm and 10 dropouts (24\%) in the study arm. Enrollment and final outcome of the study is shown in the flowchart number 1.
3.8b. Blinding

Blinding was at a single level, after determining the eligibility criteria by the risk scores (MDNS), nerve conduction studies at baseline was evaluated by assessor 1, and assessor 2 performed the nerve conduction studies for both the groups at the end of the study duration (8 weeks). Whereas, glycosylated hemoglobin was evaluated in the hospital laboratory at baseline and at 8th week for the control and study groups.
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Flowchart 1: Depicting enrollment and final outcome

Episodes with impaired consciousness requiring consultation or hospitalization, relieved by food or sugar intake
3.9. Materials

3.9a. Nerve Conduction Velocity (NCV) procedures

Clinical electro diagnosis involves the recording, display, measurements and interpretations of action potentials arising from peripheral nerves. Nerve conduction velocity (NCV) was measured using the RMS Aleron 201 electromyogram/NCV machine 2009 (Chandigarh, India). The major components of this equipment are electromyography, nerve conduction, and evoked potentials.

Parts of NCV

1. Surface electrodes
2. Filter
3. Amplifier
4. Averager
5. Display unit
6. Gain and sweep time
7. Stimulator

1. Surface electrodes:

For electro diagnostic purpose three electrodes were used, active, reference and ground. The action potential was measured between active and reference electrodes and ground electrodes served as the zero voltage reference. The surface electrodes were in the form of discs and were made of stainless steel. The surface electrodes were placed with
the help of conduction-jelly to provide an interface between the patient and the equipment.

2. **Filter**

   Filter is a device in the machine which selectively restricts the frequency domain of a signal. It usually optimizes recording by eliminating noise frequencies.

3. **Amplifier**

   Since the biological signals are very small, a variable degree of amplification is needed for the action potential before being displayed. Amplifiers help to reduce the attenuation, the impedance caused by electrodes and electrodes-skin interface. Hence amplifiers not only reduce the impedance-induced by active, reference and ground electrodes, but also minimizes and balances the action potential before it is displayed for interpretation.

4. **Averager**

   Averaging is the mechanism to extract very small signals, which are buried in large noise. It is mathematically summated, averaged and displayed. The signal to noise ratio depends upon the number of responses averaged for a nerve study. Averaging technique is typically an important tool in the study of sensory sural nerve.
5. **Display**

The neurophysiological signals were directly displayed following amplification and filtering on a display unit. It usually functions by analog to digital conversion. The continuously varying neurophysiological signals are sampled at discrete time intervals and the amplitude of the signal is converted to a number following amplification and filtering.

6. **Gain and sweep time**

The latency and duration measurements of an action potential are influenced by gain and sweep speed. On high gain or sensitivity, the latency measurements are shorter. Similarly the duration of action potential increases as the display sensitivity is increased. Increase in sweep speed results in shortening of latency, although this effect is variable and is of small magnitude.

7. **Stimulator**

For effective nerve stimulation, stimulus duration of 50-1000 µs (microseconds) is required, therefore voltage and duration controls are provided in the equipment. Two types of stimulators are routinely used; constant current (0-100 mA) and constant voltage (0-300 mV) stimulator. In the present study constant current (0-100 mA) stimulator was used and maximal and/or supra-maximal stimulation (10-30% more current that is usually required for maximal stimulation) was used which is usually recommended by various authors for nerve conduction velocity measurements (54, 55).
3.9b. Other equipment used: Apart from this for clinical assessment monofilament (5.07), knee hammer, pins (to evoke pain response), polar heart rate meter, inch tape, cotton, sphygmomanometer, treadmill were also used in the study.

3.10. Patient position

Before the procedure it was made sure that the patient is in a comfortable resting position, to allow the examiner an easy access to the lower extremities for the nerve segment being tested in the study.

3.11. Machine preparation

A few general rules were followed to ensure homogeneity throughout the testing procedure which greatly reduces the examiner related errors:

1. All recordings, reference, ground electrodes and stimulating electrodes were cleaned after each use by washing them with Sterilium. Each electrode was then dried completely before use.

2. All electrodes were electrically tested for broken wires or defective contact points. If a defect was noted it was repaired or replaced immediately.

3. Electrode site on the patient was cleaned to make it free from oil, grease and soil.

4. A thin film of electrode gel was used on each electrode to maximize conductivity.

5. All electrodes were fastened securely to the patient with tape or straps.

6. All recordings and stimulating points were marked clearly with visible ink.

7. Distances were measured with an inch tape that was closely opposed to the skin and anatomic course of the nerve.
8. The cathodes (negative pole) of the stimulating electrodes were positioned towards the active (recording) electrodes for the study.

9. The stimulus was defined with respect to the evoked potential and was graded as subthreshold, threshold, submaximal, maximal or supramaximal. In the study supramaximal stimulus was used for nerve conduction of peroneal motor nerve.

10. Latency time was measured in milliseconds (ms), was measured from shock artifact to the initial negative deflection (upward) of the response from isoelectric baseline of video display apparatus.

11. Amplitude in millivolts (mV) of the motor response was measured from isoelectric baseline to the peak of the negative phase of motor response.

12. Amplitude in microvolts (µV) of the sensory response was measured from the peak of negative phase to peak of positive phase of the sensory phase.

13. The duration in milliseconds (ms) of motor and sensory responses was measured from the initial deflection of the negative phase of the response from the isoelectric baseline to the return of the positive phase of the response to the isoelectric baseline.

14. The conduction velocity of a nerve was reported in meter/seconds (m/s). It is calculated by measuring the distance between two stimulation sites and divided by the difference in proximal and distal latency.

15. Effects of temperature on conduction velocities are well known (53, 54). Hence it was made sure that no variations were produced due to temperature, skin temperature was measured with a surface infrared device at the lower limbs and an ambient room temperature of 26-32° Celsius was maintained during the procedure.
Figure 4: Images showing the equipments used with Nerve Conduction Velocity (NCV) study

Figure 4a. Gel, Cotton and Sterilium

Figure 4b. Electrodes, Ground and Stimulator

Figure 4c. NCV Machine Set-up
3.12. **Standardization procedure for NCV evaluation**

Before starting with the study the electrophysiological evaluation of the machine was standardized for (n=15) normative data (given below) on healthy adults for sural and peroneal nerves for latency, duration, amplitude and conduction velocity. The electrophysiological evaluation was then carried out in patients with diabetic peripheral neuropathy for motor peroneal and sural sensory nerve conduction studies were performed.

**Table 8: Values for latency, duration and amplitude and conduction velocity for distal peroneal nerve among healthy adults**

<table>
<thead>
<tr>
<th>Distal peroneal nerve</th>
<th>Mean and standard Deviation (SD)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Latency</td>
<td>4.06 (0.43) millisecond</td>
</tr>
<tr>
<td>Duration</td>
<td>5.34 (0.85) millisecond</td>
</tr>
<tr>
<td>Amplitude</td>
<td>5.60 (4.44) millivolt</td>
</tr>
<tr>
<td>Conduction velocity</td>
<td>60.12 (13.53) meter/second</td>
</tr>
</tbody>
</table>
Table 9: Values for latency, duration and amplitude and conduction velocity for sural nerve among healthy adults

<table>
<thead>
<tr>
<th>Sural nerve</th>
<th>Mean and SD</th>
</tr>
</thead>
<tbody>
<tr>
<td>Latency</td>
<td>2.66 (0.44) millisecond</td>
</tr>
<tr>
<td>Duration</td>
<td>1.76 (0.57) millisecond</td>
</tr>
<tr>
<td>Amplitude</td>
<td>24.51 (17.12) microvolt</td>
</tr>
<tr>
<td>Conduction velocity</td>
<td>41.09 (4.77) meter/second</td>
</tr>
</tbody>
</table>
3.13. **Electrophysiological evaluation in the study**

3.13a. **Peroneal motor nerve conduction**

**Pick-up:** the active surface electrodes were placed over the extensor digitorum brevis (EDB) muscle in the anterior lateral aspect of the proximal midtarsal area.

**Reference:** The reference electrode was placed distally on fifth toe.

**Ground:** was placed between the site of stimulation and pick up.

**Stimulation:** distal stimulation was applied about 8 cm proximal to the pick-up, just lateral to the tibialis anterior tendon. More proximally, the nerve was stimulated just below the head of fibula as the nerve curves around the bone.

**Settings:**

- Frequency – 20 Hz to 3 kHz
- Sweep speed- 5ms/div
- Gain - 5 mV

Among the normal population reported peroneal conduction velocity below knee-segment is 46.54±4.4m/s and that across the fibular neck is 49.67 ± 8.77 m/s. The latency on the ankle stimulation is 4.55 ± 0.59 ms and distal amplitude 4.23±1.61 mV (54, 55).

3.13b. **Sural sensory nerve conduction**

**Pick-up:** the active is posterior and below the distal lateral malleolus of the fibula.

**Reference:** the reference is placed 3 cm distally.
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**Ground:** the ground is placed between the cathode and active pickup.

**Stimulation:** stimulation is applied slightly lateral to the midline in the lower third of the posterior aspects of the leg with the cathode distally. The patient feels the shock radiate to the heel and the foot. Sites 10-14 cm from the active electrodes were stimulated antidromically.

**Settings:**

- Frequency – 20 Hz to 2 kHz
- Sweep speed- 1ms/division
- Gain – 20 µV/division

In normal population the sural nerve conduction velocity is reported to be 50.9 ± 5.4 m/s and amplitude to be 18 ± 10.5 µV (54). Among Europeans mean latency was reported to be 3.5±0.25 ms for stimulation at 14 cm distance. Amplitude of evoked sensory potential was found to be: 5-30 µV. whereas the mean velocity was 37.6± 4.8 m/s (55).
Figure 5: Images showing stimulation site for Peroneal and Sural nerve respectively

Figure 5a: Stimulation of Peroneal nerve at ankle

Figure 5b: Stimulation of Peroneal nerve at neck of fibula
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Figure 5c: Stimulation of Sural sensory nerve approximately 10-14 cm from the active electrodes

Figure 6: Images showing the placement of electrodes for recording during the study for Peroneal motor and Sural sensory nerves respectively

Figure 6a. Placement of electrodes for motor Peroneal nerve

Figure 6b. Placement of electrodes for Sural nerve
3.14. Protocol for the study group

Patients with type 2 diabetes were given 2 weeks of low level exercise intensity program consisting of calisthenic exercises, before they participated in moderate intensity exercise program. A daily attendance was maintained for all the exercising individuals in the form of log book for the study group. In accordance with the physical activity guidelines for physical activity and public health (19) all the patients performed a minimum of 30-60 minutes of moderate-intensity physical activity on 5-6 days of the week. Moreover to improve glycemic control and cardiovascular risk, it is recommended that patients with type 2 diabetes accumulate a minimum of 150 min/week of moderate intensity treadmill exercises (19). Exercise was completed on at least 3 days per week, with there being no more than 2 consecutive days without training.

3.14a. Standard care and education

Standard care was given in the form of oral hypoglycemic agents and/or insulin as prescribed by the primary physician. Education was, given through posters developed by the medical hospital in accordance with the guidelines of the National Institute for Clinical Excellence (NICE) for prevention and management of foot problems in type 2 diabetes (80). Patients were given instructions for the diabetic diet by a diettian and were also reviewed for standard medical care by their physician at baseline and 8th week. Patients were instructed to adhere to the same regime of medications prescribed by their consulting physician and report any changes in medications if it took place within the stipulated period of study.
3.14b. Preparation for exercise program

Patients with type 2 diabetes are deconditioned and have limited strength and flexibility. As mentioned previously a goal of 30 minutes low intensity exercise as conditioning exercises were given single session a day for 2 weeks before moderate intensity exercise was commenced so as to not to deter these individuals from participating in the program. In patients with type 2 diabetes a good warm-up was given to promote blood supply via vasodilation of blood vessels in and around the exercising muscle. Preparation for exercise also included considerations regarding hydration and foot care. Though the patients with cardiac risks were screened and ruled out from the study still all individuals with type 2 diabetes were educated about the typical and atypical symptoms of myocardial ischemia and instructed to report these symptoms if they do occurred by any chance.

3.14c. Type of exercise:

Aerobic

Type of exercise was moderate intensity aerobic exercise on treadmill. Exercises that use a large muscle mass and those that can be performed safely offer the best results for type 2 diabetes patients. Moreover, for all the patients with type 2 diabetes, the goal of exercise is also to increase their energy expenditure, and this is directly related to the amount of muscle mass used during exercise. For this reason, moderate intensity aerobic exercises were used as it has been well documented in previous studies (19, 81, and 82) the physiological adaptations leading to enhanced glycemic control.
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Frequency

Exercising a minimum of 3 days each week was required. More frequent exercise training was also encouraged for 6 days per week to optimize glycemic control and insulin sensitivity in them.

Intensity

First the maximal heart rate of the individual was calculated with the formulae

Maximum heart rate = (220 - age)

Then Karvonen formula was used to calculate target heart rate (THR)

THR = [(Maximal Heart rate - Resting Heart rate) x % intensity] + Resting Heart rate

All exercise training was carried out in the range of 40-60% of heart rate reserve (HRR) as an adjunct to this rating of perceived exertion (RPE) (scale ranging from 6 to 20) was also carried out before, during and post exercise. The RPE scale of ‘somewhat hard’ (scale ranging to 12-13) corresponds to a HRR of 40-60 % (19, 26 and 83). RPE integrates the information coming from peripheral muscles and joints, central cardiovascular and respiratory functions, and central nervous system hence RPE is an invaluable tool to rate the exercise intensity and was incorporated in the regime for the same purpose.
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**Duration**

The duration of the exercise prescription was divided into the duration of each exercise session, as well as a total period of training required to have a desired effect on objective measures of neuropathy.

3.14d. **Session duration:**

The duration of each session was individually tailored for each patient. Patients were required to accumulate a minimum of 150 minutes of moderate-intensity exercise duration each week. Longer duration (30 to 60 minutes) was preferred typically for each session.

3.14e. **Program duration:**

As the available evidence suggests improvements in arterial stiffness, insulin resistance, and improvements in glycemic control are seen in type 2 diabetes only after 3 weeks of aerobic exercise training (19, 81 and 82). Hence program duration in the study group was kept to 8 weeks to have a desired effect on the nerve functions.

3.14f. **Warm up and cool down:**

All the patients following supervised sessions of exercises were advised to strictly adhere to 15-20 minutes of warm-up before the main stimulus phase (treadmill training). The purpose of the warm-up period before treadmill training was to slowly increase the aerobic energy production so it approaches the level of prescribed intensity. Stretching exercise for all the major muscles of the body (quadriceps, hamstring, and gastro-soleus) was performed before the sessions. A good indicator of warm-up phase was starting of perspiration which usually causes a
rise in body temperature. At this point the patients were progressed to stimulus phase of the program (treadmill training).

When stimulus phase was completed, the patients were gradually cooled down by reducing the intensity during the stimulus phase i.e. that is continuing with low intensity aerobic exercise, principle being to prevent peripheral pooling of blood. The patients were also educated about the principles and importance of warm up and cool down during the exercise sessions.

3.14g. Special considerations during training regime

1. If the blood glucose concentration was more than 250 mg/dl or ketones were present in the urine samples, exercise training was avoided; blood glucose was first controlled before the initiation of exercise regime.

2. Blood glucose level prior to exercise was evaluated. If blood glucose was less than 100mg/dl, carbohydrates in the form of simple sugars were given and training was delayed till the blood glucose levels were more than 100 mg/dl.

3. Blood sugar levels were monitored before and after exercise training to check for exercise related hypoglycemia.

4. Timing, amount and type of previous food intake was also noted before each sessions

5. Patients were also observed for blood pressure responses pre-post training.

6. A detailed drug and insulin history (onset, peak and duration of action, use and type of medications to lower the blood glucose), timing of medications administered was taken to have a check on drug and/or insulin interaction with exercise.

7. A ready source of rapidly acting carbohydrate was made available during exercise.
8. Patients in the exercise group were instructed to consume fluids before, during and after exercise.

9. Patients were instructed to practice a good foot care by wearing proper shoes and cotton socks, and were educated to inspect feet after exercise.

3.14h. Progression of exercise intensity:

As previous evidences have shown a moderate to strong correlation of RPE with VO$_2$ Max, VO$_2$ RR and HRR and efficacy of RPE as an effective tool in monitoring exercise intensity in adults have been already established, so it was used an effective tool to monitor the subjective feeling of the patient to exercise intensity (19,84,85). Hence at the initiation of the program, the patient were made to exercise with intensity of 40% of HRR and in adjunct to that they were asked to rate RPE simultaneously to the point they reach ‘somewhat hard’ (11-13 on scale) on the scale (scale range 6-20). With subsequent weeks as the patients became more conditioned to exercise program, they were made to exercise on the higher side (60%) of HRR using RPE to the point they reach ‘somewhat hard’ (11-13 on scale) on the scale (scale range 6-20).

3.15. Protocol for the control group

3.13a. Standard care and education

The same standard care protocol as of exercise group was followed for the patients in the control group to maintain homogeneity in medical care. Standard care was given in the
form of oral hypoglycemic agents and/or insulin as prescribed by the primary physician. Education was, given via posters developed by the medical hospital in accordance with guidelines of the National Institute for Clinical Excellence (NICE) for prevention and management of foot problems in type 2 diabetes (80). Patients were given instructions for the diabetic diet by a dietitian and were also reviewed for standard medical care by their physician both at baseline and 8th week. Patients were instructed to adhere to the same regime of medications prescribed by their consulting physician and to report any changes in medications if it took place within the stipulated period of study. In addition to this patients were followed-up every week till the final evaluation (8th week) through telephone to ensure they practice standard foot care protocol in their day to day life.
3.16 Evaluation of outcome measures

3.16a. Nerve conduction studies:

At baseline the nerve conduction studies (NCS) were done in the departmental laboratory by assessor 1 after clearing the eligibility criteria of the patients to determine sensory and motor abnormalities for lower-limb. At the end of 8 weeks of the study period, assessor 2 evaluated the patients for nerve conduction studies.

3.16b. Glycosylated hemoglobin:

Glycosylated hemoglobin was analyzed in the Kasturba hospital laboratory by high-performance liquid chromatography (HPLC). The evaluator analyzing the samples was not aware of the group being analyzed at baseline and at 8th week. Glycosylated hemoglobin greater than the cut off mentioned for the Indian population 6.5% was taken into account (86).

Laboratory assay: The Variant II Turbo glycosylated hemoglobin program utilizes principles of ion-exchange HPLC. The samples were automatically diluted on the Variant II Turbo Sampling Station and injected into the analytical cartridge. The Variant II Turbo Chromatographic Station dual pumps deliver a programmed buffer gradient of increasing ionic strength to the cartridge, where the hemoglobin is separated based on their ionic interactions with the cartridge material. The absorbance was measured at 415 nm. An additional filter was provided at 690 nm to correct the background absorbance.

Recommendations from the American Diabetes Association (ADA) includes the use of HbA1c to monitor glycemic control in type 2 diabetes, using a cutoff of 6.5% - 7% (18).
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3.16c. Scores and questionnaires:

MDNS consists of a clinical neurological examination which is easily conducted in routine clinical practice for staging of DPN. Vibratory threshold perception, pain, and light touch were assessed with a 128Hz tuning fork, a pin, and a 10 gm filament, respectively. In the present protocol, the 10 gm filament is applied to the dorsum of the great toe, and the patient is asked to respond "yes" if he or she feels the filament. Eight correct responses out of 10 applications is considered normal (score of 0); 1-7 correct responses indicate reduced sensation (score of 1); and no correct answers translate into absent sensation (score of 2). Tendon reflexes are scored as 0 for normal, 1 for abnormal, and 2 for absent responses. Muscle strength is scored as 0 for normal, 1 for mild to moderate, and 2 for severe weakness, while complete loss of strength is scored as 3. Study done by Feldman et al found that MDNS had a moderate correlation of 0.59 (p<0.05) with nerve studies and was equally useful for staging DPN (60).

Neuropathy quality of life is a 35 item Neuropathy- Specific Quality of Life instrument (NQOL) is a hierarchically organized scale that assesses patient’s subjective reports of functioning and quality of life in six specific domains. Each domain is assessed with items that measure specific somatic experiences, social and personal dysfunctions and emotional states, and end with an overall assessment of quality of life or satisfaction with experiences in that domain. Thirteen items assess specific somatic experiences in three domains: i.e., Pain (items 1-7), Lost/reduced feeling (items 8-10); and Diffuse sensory-motor symptoms (items 11-13). Specific functional, social and emotional experiences are assessed in three domains with an additional 14 items: Restrictions in activities of daily living (items 14 – 16), and Disruptions in social relationships (items 17-20), and Emotional distress (items 21- 27). The frequency of these
experiences, somatic, social and affective, were reported on 5 point scales (never, to all of the time). A participant's score for a domain is the mean of the items in that scale with higher scores representing more severe symptoms or greater disruption in functioning in day to day living. NQOL’s reliability has been already been established and is found to be a valid measure to address the impact of peripheral neuropathy on quality of life (40). The content and construct validation of the NQOL was done by a panel of institutional experts, for identifying its suitability, comprehensibility for addressing the issues pertaining to diabetic foot care in India. Feedback from the diabetic population was also included in the initial draft for validating the NQOL into the regional language (Kannada) for better interpretation and categorization of the questions so as to have compliance with the Indian social and cultural context.
3.17. Data analysis

Log transformation was applied to skewed variables and geometric mean and geometric standard deviation was reported as a measure of central tendency and dispersion for all the continuous variables (age, duration of diabetes, medications and insulin, anthropometric measures and primary outcome measures) and categorical variables were expressed as frequency. Repeated measures of Analysis of Variance (RANOVA) were used to analyze the changes in primary outcome measures at multiple time periods between the exercise and the control groups. A $p$ value of less than 0.05 was considered statistically significant and the tests were carried out using Statistical Package for the Social Sciences (SPSS) 15. For primary outcome measures in the study degrees of freedom 1 and 2 (Df1, Df2), F test statistic value and $p$ values were reported for RANOVA. The Pearson correlation coefficient was used to examine the relationship between different variables in the study, a $p$ value less than 0.05 was considered statistically significant.