5.1 PHASE - I

5.1.1 Estimation of overall musculoskeletal complications in T2DM

In the present study, a total number of 539 subjects with T2DM were recruited and a total number of 324 (60.11%) subjects were reported with musculoskeletal complications. In a study by Suzan Attar in 2012, it was reported that 18% prevalence of musculoskeletal complications in 252 T2DM subjects screened, but the limitation of the subject field was only shoulder and hand manifestations were screened. (Attar, 2012) Similar to present study, a study by Douloumpakas who screened for musculoskeletal complications using Short Musculoskeletal Function Assessment Questionnaire (SMFA) found the prevalence of 82.6% musculoskeletal complications in T2DM. Degenerative, non-inflammatory abnormalities like Degenerative spondylosis, Carpal tunnel syndrome, Diabetic Cheiroarthropathy etc. exhibited a high prevalence rate among these disorders than inflammatory disorders. In line with the study by Douloumpakas, in our study, we found a high prevalence of musculoskeletal complications like low back pain and shoulder adhesive capsulitis.

A possible reason for musculoskeletal complications in T2DM: Although the precise etiology of T2DM associated musculoskeletal complications remains uncertain, there is evidence that abnormal collagen deposition in the connective tissues alters the structural matrix and the mechanical properties of these tissues. (Rosenbloom et al., 1996) Some musculoskeletal complications seem to be a consequence of neuropathic arthropathy and some share pathological mechanisms with microvascular disease. (P. E. T. Arkkila et al., 2003) Hyperglycemia and other diabetes-associated metabolic disturbances may lead to conditions such as: Nonenzymatic glycosylation of proteins resulting in AGE formation.
and connective tissue stiffening, nerve damage (Neuropathy), vascular damage (blood vessel), hyperuricaemia, reduced bone density, low-grade chronic inflammation and abnormal levels of insulin and insulin-like growth hormone. The insulin-like growth factor and hyperinsulinemia associated with T2DM may contribute to skeletal anomalies. Insulin stimulates collagen synthesis and influences the proteoglycan composition of bone and cartilage, whilst insulin-like growth factors (such as IGF-1) stimulate osteoblast activity. (Kemink et al., 2000)

5.1.1.1 Low back pain

Low back pain was reported in 31.5% T2DM subjects (Figure: 24). It is the most common musculoskeletal disorder in developing countries and is considered to be a leading cause of work-related disability. (Jenkins et al., 2002; Storheim & Zwart, 2014) In a study conducted by O.A. Idowu in 2015 documented a prevalence of 46.2% low back pain in T2DM subjects (Idowu et al., 2015) whereas the study by Maghsoud Eivazi et al reported a 12 month low back pain prevalence of 63.4% among 317 patients with T2DM (Eivazi et al., 2012).

A possible reason for low back pain in T2DM: The possible reason for low back pain could be due to a strong effect on a micro or macrovascular network of the vertebrae and spinal degeneration, a long-term involvement in this condition would be capable of causing severe degenerative changes in the low back. (Eivazi et al., 2012) Another possible reason could be due to glycosylation of the proteins, microvascular abnormalities which damage blood vessels and nerves; and collagen accumulation in periarticular structures which
results in changes in connective tissues, and also the weakness of lower back extensor muscles predisposing the lumbar vertebrae into structural and functional alterations.

5.1.1.3 Shoulder adhesive capsulitis

Shoulder adhesive capsulitis is a rheumatological condition commonly seen in the normal population, whereas diabetes mellitus is considered to be one of the risk factors for developing shoulder adhesive capsulitis. (Arkkila et al., 1996; Jenkins et al., 2002) It is documented that subjects with T2DM have 5 times more the risk for developing shoulder adhesive capsulitis. (Lebiedz-Odrobina et al., 2010) The prevalence of shoulder adhesive capsulitis in diabetic patient’s ranges between 10 and 29 % as compared with 3–5 % of the age-matched controls. Even though the prevalence was more eminent in several studies, in the present work, we found adhesive capsulitis in 4.6% T2DM subjects (Figure 24).

A possible reason for shoulder adhesive capsulitis in T2DM: The exact mechanism of pathology of shoulder adhesive capsulitis remains unclear, but several abnormalities in biochemical factors, including increased glycosylation of collagen protein, altered collagen synthesis, altered microcirculation to the shoulder joint, increased production of advanced glycated end (AGE) products which alter the intracellular and extracellular function which precipitate into adhesive capsulitis at a time. (S. J. Thomas et al., 2007)

5.1.1.4 Fatigue

Subjects with T2DM suffer from serious health problems that associate to physical, mental, and social prospects of their life. (Fritschi et al., 2010) Fatigue, a common symptom among T2DM patients, may be the direct result of physiological processes, treatment, and complications associated with long-term T2DM. According to previous
studies, up to 60% of patients with T2DM experience fatigue symptoms. (Drivsholm et al., 2005) Whereas, in the present study, we found 20.6% of the T2DM subjects were suffering from fatigue.

**A possible reason for fatigue in T2DM:** One likely reason for fatigue in T2DM is alterations in blood glucose levels. Altered blood glucose metabolism may result in acute and chronic hyperglycemic episodes, hypoglycemia or blood glucose fluctuations. These alterations may affect fatigue separately or together. The presence of short- and long-term complications of T2DM and their symptoms, including symptoms of hypo- or hyperglycemia, cardiac disease, neuropathy, or retinopathy, has likewise been linked with increased fatigue. (Morsch et al., 2006; Weijman et al., 2004) Blood glucose fluctuations can be one of the reasons for the fatigue. A study of non-insulin-treated adults with T2DM (n = 856) revealed exaggerated postprandial glucose excursions (in excess of 40 mg/dl) from pre-meal blood glucose values in the majority of subjects. These findings were consistent, even in subjects with HbA1c values in the satisfactory range (< 7.0%). (Deray et al., 2004) Recent evidence suggests that these glucose fluctuations during the postprandial period may be strong triggers for inflammatory markers and oxidative stress, thought to play a key role in the development of diabetic vascular complications. (Monnier et al., 2006) Oxidative stress and fatigue were studied in patients with chronic fatigue syndrome. In a control-matched, cross-sectional study of 47 adults with chronic fatigue syndrome, increased markers of oxidative stress, including isoprostanes and oxidized low-density lipoproteins, were linked with chronic fatigue symptoms. (Kennedy et al., 2005)
5.1.1.5 Plantar fasciitis

Studies reported that in subjects with T2DM, the thickness of plantar fascia is altered leading to abnormal loading on the foot affecting the foot biomechanics. (Abate et al., 2012; Craig et al., 2008; Kumar et al., 2015) In a study by Kumar et al in 2015, assessed T2DM subjects to identify the thickness and cross-sectional area of intrinsic foot muscles and plantar tissue which includes plantar fascia, plantar skin and plantar fat pad. It was concluded that subjects with T2DM presents with reduced thickness of the plantar fascia, plantar skin and plantar fat pad which puts the foot at risk for high plantar pressures. Whereas in another study by Michele Abate et al found the increased thickness in plantar fascia, which was contradictory to the previous study by Kumar et al. They also documented that the increased thickness of the plantar fascia was associated with adiposity. (Abate et al., 2012) These altered structural and changes and increased plantar pressure may lead to repeated injury to the plantar fascia leading to plantar fasciitis.

**A possible reason for plantar fasciitis in T2DM:** The possible reason could be due to loss of thickness of plantar fascia caused due to increased plantar pressure on the foot. (C. G. S. Kumar et al., 2015) This was confirmed by a study done by Abouaesha et al, documented that a strong inverse relationship between the plantar tissue thickness and dynamic foot pressure. A repeated plantar pressure leads to microtrauma at the plantar fascia origin leading to fascitis.(Abouaesha et al., 2001) Another possible reason could be due to barefoot walking as a traditional or cultural practice. Most of the people in India don’t use footwear indoors and this could increase the plantar pressures under the foot leading to increased stress on the plantar tissue leading to micro trauma and inflammation of the plantar fascia.
5.1.1.6 Carpel tunnel syndrome, duputryens contracture and flexor tenosynovitis

Several studies documented on musculoskeletal manifestations in T2DM but commonly focused on hand manifestations. Carpel tunnel syndrome, duputryens contracture and flexor tenosynovitis are the most commonly studied hand complications. In the present study, we didn't see much of these complications affecting the T2DM population. Carpel tunnel syndrome was found in 0.6% T2DM subjects, deputryens contracture and flexor tenosynovitis was seen in 0.2% of the T2DM population respectively (Figure 24). Studies have documented that the prevalence of carpal tunnel syndrome in T2DM ranges between 11-25% being more common in women. (Papanas & Maltezos, 2010) Various studies have reported a prevalence of 21-63% duputreyens contracture in T2DM in the contract of 5-22% of the non-diabetic population.

Studies reported prevalence of trigger finger in patients with DM ranges from 5% to 36% in those with T1DM or T2DMas compared with 2% in the non-diabetic subjects. (Cagliero et al.,2002) Another interesting report from India by Sarkar et al. reported that the trigger digits can be seen in 1:20 (cases with trigger digits: All diabetic patients). (Sarkar RN et al., 2003) However, some other reports such as that by Aydeniz et al show no significant increase in the incidence of this condition in T2DM subjects. (Aydeniz, Gursoy, & Guney, 2015)

A possible reason for the Carpel tunnel syndrome, duputryens contracture and flexor tenosynovitis in T2DM: The possible reason could be the due formation of AGE products or the impaired degradation of byproducts, it could be indirectly related to the vasculopathy and neuropathy commonly complicating the primary disease, or finally, it could be attributed to a combination of factors. (Douloumpakas et al., 2007)
5.1.2 Estimation of foot complications in T2DM

Foot complications are considered to be the common complications seen in subjects with T2DM with uncontrolled blood glucose levels and long standing T2DM. In the present work, a total number of 539 subjects with T2DM were screened for complications. Out of them, a total number of 362 (67.1%) cases were reported with foot complications. In a study, TS Ferguson, reported an overall prevalence of foot complications by 12% and foot complications was significantly associated with duration of diabetes. (Ferguson et al., 2013) Whereas another study in Taiwan reported foot complications by 2.9% among T2DM subjects. (Tseng, 2003) A study by Khalid Al-Rubeaan, reported 3.3% prevalence of foot complications among 62,681 T2DM subjects screened and also documented that foot complications are increased with age and duration of T2DM. (Al-Rubeaan et al., 2015)

A possible reason for foot complications in T2DM: The possible reason for developing foot complications include neuropathic, vascular, and immune system components, which all show a base relationship with the hyperglycemic state of diabetes. (Clayton & Elasy, 2009; Wolf, 2004) Hyperglycemia produces oxidative stress on nerve cells and leads to neuropathy. (Clayton & Elasy, 2009) Additional nerve dysfunction follows from glycosylation of nerve cell proteins, leading to further ischemia. These cellular changes manifest in motor, autonomic, and sensory components of neuropathic foot complications. Damage to the motor neurons of the foot musculature may lead to an imbalance of the intrinsic foot muscles, anatomic deformities, and lead to increased plantar pressure under the foot which further lead to callus formation and ulcers. (C. G. S. Kumar et al., 2015)
Damage to autonomic nerves impairs sweat gland function, and the foot may develop decreased the ability to moisturize skin, leading to epidermal cracks and skin breakdown. T2DM subjects with peripheral neuropathy may not notice foot injuries because of decreased peripheral sensation. Because the blood supply required to heal a diabetic foot ulcer is greater than that needed to maintain intact skin, chronic ulceration can develop. (Sumpio, 2012, C. G. S. Kumar et al., 2015) Vascular changes that lead to diabetic foot ulcers correlate with hyperglycemia-induced changes in the peripheral arteries of the foot and begin on the cellular level. (Clayton & Elasy, 2009) The result is vasoconstriction and plasma hypercoagulation in peripheral arteries leading to ischemia and increased the risk of ulceration.

5.1.2.1 Diabetic peripheral neuropathy

The prevalence of DPN ranges from 7% in subjects within 1 year of T2DM duration and 50% in subjects with a duration of T2DM more than 25 years. (Yagihashi et al., 2011) In the present study, 44% of the T2DM subjects were reported with DPN (Figure 25). Distal and sensory predominant nerve fiber degeneration, axonal loss and endoneurial microangiopathy are the characteristic findings in DPN. (Tsitouras, States, & Control, 2015). Based on this anatomical condition, studies documented that microvascular injury is the most causal factor for focal fiber loss of distal predominant axonal neuropathy in T2DM. (Yagihashi et al., 2011) However, this explanation is too simplistic and does not explain why hyperglycemia and duration of diabetes are crucial for its occurrence.

A possible reason for diabetic peripheral neuropathy in T2DM: Studies reported controversial results questioning whether there is any predominance for the involvement of
small fibers in early DPN. Questions on this issue were further raised by the report that the loss of nerve function was not universally demonstrated, indicating that microangiopathy does not always account for the fiber loss. Malik et al. showed that subjects who did not have clinically evident neuropathy at the time of nerve biopsy, but who showed high-grade microangiopathic changes of endoneurial microvessels later, developed neuropathy, whereas the patients without microvessel changes did not develop neuropathy. Therefore, the possible reason for DPN could be due to microangiopathy which affects the vasa nervorum, a blood supply to the nerves leading to loss of nerve function.

Another possible reason for DPN could be due to hyperglycemia. Hyperglycemia not only activates the sorbitol accumulation with a subsequent increase in cellular osmolarity, but it also shunts to the hexose pathway, producing oxidative stress and the formation of advanced glycation end products. (Vincent et al., 2011) Damage to peripheral nerves results in hyperexcitability in the primary afferent nociceptors. This damage leads to hyperexcitability in central neurons and the generation of spontaneous impulses within the axons as well as the dorsal root ganglion of these peripheral nerves. (Baron, 2000)

5.1.2.2 Skin complications

T2DM affects the foot in three major systems which include autonomic neuropathy, sensory neuropathy, and motor neuropathy. An autonomic nervous system which regulates perspiration at the periphery is affected in long-standing T2DM, leading to dry skin, fissures, and callus formation. In the present study, we found the very high prevalence of skin manifestations. Dry skin was reported in 75.1% of the T2DM subjects, fissures were reported in 41.0% and callus was reported in 32.3% of the T2DM subjects.
Skin manifestations in T2DM were reported to be very common ranging from 47.5 – 91.2%. (Demirseren et al., 2014; Hosseini et al., 2010; Shahzad et al., 2011) It is estimated that more than 75% of DM subjects suffer from a skin condition (Demirseren et al., 2014). In a study conducted on 750 subjects with T2DM found that the most common skin manifestations were cutaneous infections (47.5%), xerosis (26.4%), and inflammatory skin diseases (20.7%) as a result of autonomic neuropathy. Subjects with T2DM are more likely than those with T1DM to develop cutaneous manifestations. Dry skin and other skin conditions are closely linked to each other. In fact, the first sign that a subject has diabetes is usually some sort of skin disorder. (Demirseren et al., 2014)

**A possible reason for dry skin and fissures in T2DM:** The possible reason could be due to uncontrolled blood glucose levels which can reduce blood flow to the skin as well as damage blood vessels and nerves. Decreased blood circulation can lead to changes in the skin collagen, altering its texture, appearance, and ability to heal. As a result of damage to the autonomic neuropathic system, the skin endothelial cells gets damaged and this may even reduce its ability to sweat which leads to dry skin, fissure and callus formation as well as a decrease in ability to sense temperature and pressure. (J. Petrofsky, Berk, & Al-Nakhli, 2012)

**5.1.2.3 Callus, hammer/claw deformity of toes**

Loss of sensation, loss of proprioception and toe deformities caused due to long standing diabetes, uncontrolled blood glucose and peripheral neuropathy are considered to be the major risk factors for the development of callus and deformities. (M. E. Fernando et al., 2014a) In line with the results from Fernando, we also found high prevalence of callus formation in subjects with T2DM.
Several factors may be responsible for the callus formation where DPN plays a major role. Loss of sensation as sensory neuropathy and motor neuropathy leading to wasting or atrophy of intrinsic foot muscles causing deformities like hammer toes and claw toes. These deformities are found to be a significant factor in the structural foot changes that often result in an increase in pressure in certain areas of the plantar aspect of the foot leading to callus formation which further increases the plantar pressures. (Smith et al., 2000)

In a study conducted by William R. Ledoux, on high risk 398 diabetic population reported that 46.7% of the diabetic population had hammer/claw toe deformity. (Pai & William R. Ledoux, 2010) whereas in another study conducted in Iraq concluded that 5.4% hammer/claw toe deformity were observed in of diabetic population which is in line with the present study where we found 5.9% of T2DM subjects with hammer toes (Figure 25). (Mansour & Imran, 2006) Very high prevalence of 45.43% of hammer/claw toe deformity were reported in a study by Müulescu et al on the diabetic population with distal symmetric polyneuropathy. (Miulescu et al, 2014)

A possible reason for callus and toe deformity in T2DM: The possible reason for callus formation and toe deformities include sensory neuropathy and motor neuropathy as a result of peripheral neuropathy. Due to loss of sensation in the feet, patients tend to keep the feet in contact with the ground for a longer period (Increased step duration) to maintain the center of gravity within the base of support. This alteration increases the plantar pressure under the feet and as a combined effect of autonomic neuropathy and sensory neuropathy skin loses its normal function leading to increased plantar pressure and callus formation.
As a result of motor neuropathy, intrinsic foot muscles undergo atrophic changes leading to clawing of toes. Several studies on structural analysis of intrinsic foot muscles documented that T2DM subjects with peripheral neuropathy are seen with atrophy of intrinsic foot muscles leading to clawing of toes and anterior translation of plantar fat pad. (SA Bus et al., 2009; Sicco a. Bus et al., 2002; Kumar et al., 2015; Severinsen K et al., 2007) Another possible reason for formation of callus and toe deformities could be due to walking barefoot indoors as a cultural practice in India and using inappropriate footwear’s put the foot into risk with increased plantar pressures and direct injury to the plantar surface while walking barefoot.

5.1.2.4 Plantar ulcers

Foot ulceration is the most common complication affecting approximately 15% of diabetic patients during their lifetime. (Shankhdhar et al., 2008) Whereas, in the present study, only 5.2% subjects were reported with foot ulceration (Figure 25). Studies have indicated that diabetic subjects have up to 25% lifetime risk of developing foot ulcers. (Singh et al., 2005) Similar to our results, In the UK and the USA the prevalence of foot ulceration due to diabetes has found to be 5-7%. (Kerr, 2012)

In a developing country like India, the prevalence of diabetic foot ulcers is on the increase. In a study conducted by Shahi et al., on the T2DM population in North India found that 14% of the diabetic population had foot ulcers among 87% of T2DM subjects. They also found that in the diabetic foot ulcer group 70.10% of the population belonged to rural areas and 29.9% were from urban areas stating that the risk of diabetic foot ulcers was high in rural population as compared to the urban population. (Shahi et al., 2012)
whereas another study on South Indian population documented that 41.51% of the diabetic population were with nonhealing diabetic ulcers. (Abraham et al., 2015) Several factors are considered to be risk factors for the development of diabetic foot ulcers which varies from population to population. A study conducted by Vijay Vishwanathan among 613 T2DM population from Tanzania, Germany, and India, found that peripheral neuropathy was a common risk condition among patients in all 3 centers. PVD was frequent in Germany, while in Tanzania and Chennai, India, it was far less common. A lesser prevalence of PVD, and yet the higher prevalence of amputation rate among Indians, was noted when compared with those in Western countries because of progressive infection. (Viswanathan, 2007)

**A possible reason for foot ulcers in T2DM:** This could be due to several social and cultural practices such as barefoot walking, inadequate facilities for diabetes care and education, and poor socioeconomic conditions. (Dixit et al., 2011) Another possible reason for the formation of foot ulceration includes DPN and PVD. Subjects with loss of sensation in the feet are at very high risk for ulcer formation. Most of the rural population in India, walk bare foot indoors and outdoors. This might be a very important factor as feet gets injured through burns, sharp objects and stones as the subjects may not be aware as a result of loss of sensation.

In fact, about 50% of T2DM subjects will primarily display DPN, 20% of T2DM subjects with foot ulcers will primarily display inadequate peripheral arterial supply (also called peripheral arterial disease, PAD) and about 30% will display a combination of both conditions (i.e., neuro ischemia). The prevalence of peripheral arterial disease among those
with foot ulcers has recently been shown to be increasing and now the majority likely has PAD or neuro ischemia. (Margolis et al., 2011)

5.1.3 Association between duration of T2DM and foot complications

Studies reported that the foot complications are associated with several factors like obesity, peripheral vascular diseases and uncontrolled blood glucose levels, duration of diabetes mellitus, HbA1c and age. Whereas, duration of T2DM is considered to be the most common risk factor. (Lavery et al., 2006; Nehring et al., 2014; Rao, D, & D, 2015; Shahbazian et al., 2013; Shahi et al., 2012)

In the present study, stepwise multivariate analysis was performed to find the association between the duration of T2DM and foot complications and we found foot complications like fissures and callus were associated with T2DM duration more than six years (Table 5). Similar to our study, a study by Rao et al documented that the prevalence of peripheral neuropathy and autonomic neuropathy increases as the duration of T2DM increases. In their study, out of 51 subjects with peripheral neuropathy, 7 subjects had <5years duration and 44 subjects had >5years duration of diabetes. Autonomic neuropathy was seen in 8 subjects with <5years duration and 24 subjects with duration >5years. (Rao et al., 2015) In the present study, we found a significant risk association between peripheral neuropathy, fissures, and callus with duration of T2DM 1-5years (p=0.003), >11years (0.015) and 1.5years (0.003) respectively.

A statistically significant association between peripheral neuropathy, fissures and callus with duration of T2DM 1-5years (p=0.003), >11years (p=0.015) and 1.5years (p=0.003) respectively was observed in the present study. Fissure was 1.86 times more
likely to be associated with duration of T2DM 11-15 years and 2.18 times risk association with duration of T2DM >15 years. Whereas callus and peripheral neuropathy was 0.465, 0.458 times more likely to be associated with duration of T2DM 6-10 years respectively (p=0.003).

Even though we didn't find much association other than fissures, in a study by MOe et al, documented a correlation between fissures and autonomic neuropathy, authors reported that decreased perspiration due to autonomic neuropathy can lead to dry skin and fissure development in subjects with a long duration of diabetes mellitus. Since the plantar skin does not have sebaceous glands, dryness is more likely. Decreased perspiration due to autonomic neuropathy decreases stratum corneum moisture content, which in turn can lead to fissures.(Oe et al., 2012) In another study by Rao et al., 2015 reported among 51 T2DM subjects, peripheral neuropathy was observed in 7 subjects with duration of T2DM <5 years and 44 subjects had >5 years. Autonomic neuropathy was observed in 8 subjects with duration of T2DM <5 years and 24 subjects with duration >5 years.
DISCUSSION PHASE-II
5.2 PHASE II

Prevalence of T2DM progressively affects younger and middle-aged population worldwide. The prevalence of DM worldwide was estimated 415 million in 2015 and is expected to rise to 642 million by 2040 (IDF 2015). Population growth, aging, urbanization, changing lifestyle, reduced physical activity and dietary habits signify in global epidemiology for T2DM and its complications which are on the verge to rise in the Indian population. (Cheema et al., 2014) Foot complications are considered to be life-threatening complications if it’s not screened and managed at the early stage of the disorder may lead to serious complications like ulcers and finally amputations. Though many drug therapies are available for the management of T2DM, lifestyle modification and self-foot care plays a major role in preventing foot complications.

On the contrary, moderate intensity (Heart rate reserve 40 - 60% or rating of perceived exertion (RPE) - somewhat hard) aerobic exercise of 30 minutes duration per session for 12 weeks, self-foot care can play a vital role in controlling blood sugar levels and in the control of foot complications.

Considering this need for controlling foot complications, in the present study we have developed a structured foot health program which includes aerobic exercises, foot exercises, self-foot care and education. Lifestyle intervention programs consisting of glucose control through medication, exercise prescription with or without dietary modulation, self-foot care have found to be very effective in diabetes control and prevention of complications. Several published guidelines are available to support diabetes care providers in caring for patients with T2DM. These include recommendations from the
American Diabetes Association (ADA), American college of Sports Medicine (ACSM), the World Health Organization (WHO), the American Association of Clinical Endocrinologists (AACE). These guidelines recommend on the importance of exercise in controlling diabetes and preventing it from further progressing to complications. As exercise plays a major role in modulating T2DM and preventing complications, it is recommended to get exercise prescribed by a health care provider after undergoing a pre-exercise evaluation to rule out diabetes-related complications. The American College of Sports Medicine recommends, at least, 150 minutes per week of moderate intensity aerobic activity, 30 minutes of vigorous-intensity aerobic activity, or a combination of both for adults.

In the present study, there are plausible reasons that may lead to a change in biochemical and biomechanical characteristics of foot in subjects with T2DM. The effect of structured foot health program on blood sugar level, peripheral neuropathy, intrinsic foot muscles, foot biomechanics (Kinetics and kinematics) and quality of life in T2DM will be outlined in detail.

5.2.1 Effect of structured foot health program on blood glucose levels

T2DM is associated with severe long-term complications including microvascular complications such as retinopathy and nephropathy, macrovascular complications such as coronary artery disease and stroke, with an increased risk of premature death. Achieving and maintaining appropriate glycemic control is vital to the management of these co-morbidities and this aim has traditionally been obtained using novel pharmacological solutions, dietary intervention and physical activity. (ADA, 2013; Nayak et al., 2005)
For decades, exercise has been considered a cornerstone of diabetic management along with diet and medication. Aerobic exercise refers to activities such as walking or jogging with continuous, repetitive movement of large muscle groups for at least 10 minutes at a time. Aerobic exercise may modify the insulin action of each fiber without increasing fiber size. (Stewart, 2004) It is well known that regular aerobic exercise produces positive effects in patients with T2DM, resulting in improved glycemic control and the reduction of diabetic complications. The present study was designed to assess and compare the effects of aerobic exercises on blood sugar levels and glycemic control or the reduction of diabetic complications. As a therapeutic intervention of diabetes, exercise has previously been evaluated in numerous studies regarding its type, duration, intensity, and frequency.

HbA1c is an important indicator of glycemic control. Good glucose control at or below 7% can reduce the long-term complications by up to 76%. (Shenoy, Arora, & Jaspal, 2009) The changes of HbA1c values in our groups confirm the previous positive findings. In our study, HbA1c values decreased by 0.95% (from 9.20% to 8.25%) in the experimental group with aerobic exercises, which is greater than MCID value 0.9% HbA1c whereas in the control group there was only 0.05% (from 9.80% to 9.75%) changes in HbA1C was reported (Table 8). This possible change in the HbA1c reached the MCID value 0.9% in experimental group could be due to combined effect of physician prescribed management which consists of oral hypoglycemic agents, diabetic diet along with structured foot health program which consists of aerobic exercises, intrinsic foot muscle strengthening and foot care. Our findings supported by Boule et al, reported that exercise reduces HbA1C by approximately 0.99% an adequate reduction to improve glycemic control. (Boul et al., 2003) In a study by Yavari et al also found a similar reduction in
HbA1c of 0.73% in an experimental group whereas in the control group the HbA1C elevated to 0.28%. (Yavari et al., 2010)

Several studies compared the effects of aerobic exercises between resistive exercises and concluded that aerobic exercises are more effective in reducing the HbA1C levels. A systematic review by Umpierre et al, aerobic and resistance exercises reduced HbA1c by 0.73% and 0.57%, respectively. (Umpierre et al., 2011) Similarly, in another study it was found that HbA1C values decreased by 1.33%, 0.55%, and 1.74% in the aerobic, resistance, and combined exercise training groups respectively, whereas, it had a 0.2% elevation in the control group. (Yavari et al., 2012) This improvement of HbA1C may provide a great benefit at least to patients with worse glycemic control. The maintenance of normal blood glucose at rest and during exercise depends largely on the coordination and integration of the sympathetic nervous and endocrine systems. (Suh, Paik, & Jacobs, 2007) Contracting muscles increase uptake of blood glucose, although blood glucose levels are usually maintained by glucose production via liver glycogenolysis and gluconeogenesis and mobilization of alternate fuels, such as free fatty acids. (Suh et al., 2007; Wahren & Ekberg, 2007)

A possible reason for reduction in blood glucose levels: Several factors influence utilization of glucose and lead to a reduction in HbA1C levels, but the most important are the intensity and duration of aerobic exercise. (Galbo et al, 2007; Houmard et al., 2004; Manetta et al., 2002; Sudip Bajpeyi et al., 2009)

Fuel metabolism during exercise (Fuel mobilization, glucose production, and muscle glycogenolysis): Any activity causes a shift from predominant reliance on free fatty acid at
rest to a blend of fat, glucose and muscle glycogen with a small contribution from amino acids. With increasing exercise intensity, there is a greater reliance on carbohydrate as long as sufficient amounts are available in the muscle or blood. (Boon et al., 2007; Borghouts et al., 2002) Early in the exercise, glycogen provides the bulk of the fuel for working muscles. As glycogen stores become depleted, muscles increase their uptake and use of circulating blood glucose, along with free fatty acid released from the adipose tissue. (Watt et al., 2002) Intramuscular lipid stores are more readily used during longer-duration activities and recovery. (Hwang & Weiss, 2014; Pruchnic et al., 2004) Glucose production also shifts from hepatic glycogenolysis to enhanced gluconeogenesis as the duration increases. (Suh et al., 2007; Wahren & Ekberg, 2007)

**Insulin-independent muscle glucose uptake during exercise:** There are two well-defined pathways that stimulate glucose uptake by the muscle. At rest and postprandially, its uptake by the muscle is insulin dependent and serves primarily to replenish muscle glycogen stores. During exercise, muscle contractions increase blood glucose uptake to supplement intramuscular glycogenolysis. As the two pathways are distinct, blood glucose uptake into working muscle is normal even when insulin-mediated uptake is impaired in T2DM. (Braun et al., 2004) Muscular blood glucose uptake remains elevated post exercise, with the contraction-mediated pathway persisting for several hours and insulin-mediated uptake for longer. Glucose transport into the skeletal muscle is accomplished via GLUT proteins, with GLUT4 being the main isoform in muscle modulated by both insulin and contractions. (Holten et al., 2004) Insulin activates GLUT4 translocation through a complex signaling cascade. (Zorzano et al., 2002) Contractions, however, trigger GLUT4 translocation at least in part through activation of 5-AMP–activated protein kinase. (Musi et al., 2001)
5.2.2 Effect of structured foot health program on peripheral neuropathy in T2DM

Diabetic peripheral neuropathy is the common complications which affects both sensory, motor and autonomic nervous system. The prevalence of DPN ranges from 7% in subjects within 1 years of T2DM and 52% in subjects with a duration of T2DM more than 25years. (Yagihashi et al., 2011)

DPN 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 in the family. (Gore et al., 2005) Though many pharmacological therapies are available for the management of DPN, but none of them have promising results and have added adverse effects on an individual. (Gimbel et al, 2003, Wong et al., 2007)

On the contrary moderate intensity (Heart rate reserve of 40-60% or rating of perceived exertion (RPE) -somewhat hard) aerobic exercise of 30 minutes duration per session for 12 weeks can play a vitally important role in the control of diabetic peripheral neuropathy. In the present study, we have used Michigan neuropathy screening instrument (MNSI) score and Vibration perception threshold (VPT) to find the presence of DPN. Based on ADA guidelines, VPT scores more than 25V and MNSI A score >7 and MNSI B score > 2.5 is considered as presence of DPN. For better understanding we have categorized DPN into mild, moderate and severe DPN. Whereas VPT scores 15 – 24V as mild DPN, 25-35V as moderate DPN and >36V as severe DPN. MNSI score 2.5 – 4 as mild DPN, 4.5 – 6 as moderate DPN and >6.5 as severe DPN. A significant reduction in VPT was reported in the experimental group, moderate neuropathy (23V and 20V) reduced
to mild or no neuropathy (10V and 16V) whereas in control group VPT was increased from mild or no neuropathy (18 V and 16v) to moderate neuropathy (23 V and 23v). In Michigan neuropathy screening instrument score (MNSI), the experimental group showed an improvement (<0.001) after the intervention i.e. baseline MNSI A score was 6 which reduced to 2 at the 12th week and MNSI B score was 3 which reduced to 2(<0.001). Whereas in the control group, with MNSI A score was 2 at the baseline which increased to 5 and in MNSI B was 2 at the baseline and increased to 4.50 at the 12th week (<0.001).

**A possible reason for change in the Diabetic peripheral neuropathy symptom:**
Adaptations due to moderate intensity aerobic exercise may cause restoration of peripheral nerve functions by inhibition of aldose reductase (AR) leading to sparing of NADPH (Nicotinamide Adenine Dinucleotide Phosphate hydroxide) which may then participate in the synthesis of nitric oxide thereby relieving the nerves of their hypoxic state. Hyperglycemia can also promote superoxide production as a consequence of glucose auto-oxidation, formation of advanced glycation end products, and activation of protein kinase C, which leads to inactivation of Nitric Oxide (NO) production which is an important mechanism of endothelial dysfunction in DPN. (Chmetterer et al., 2002; Sheetz & King, 2002) There is evidence that aerobic exercise training has effects on endothelial dysfunction and vascular distensibility in T2DM. (Green et al., 2004) Hence, it may be hypothesized from the previous evidence that an improvement in endothelial-derived NO may also cause restoration of nerve functions in DPN population. The aerobic adaptation due to aerobic exercise may cause inhibition of excessive production of protein kinase C and activation of endothelial-derived NO. Another important possible reason for change in the symptoms of peripheral neuropathy could be die to the added effect of exercise induced
glycemic control. This might have reversed the metabolic changes which occurs as a result of hyperglycemia which is a key factor for development of peripheral neuropathy.

Another major important component and cornerstone of structured foot health care is patient education and self-foot care. Most of the foot complications are preventable through proper care. Poor knowledge of foot care and poor foot care practices were identified as important factors for foot complication in T2DM subjects. (Chandalia et al., 2008) Evidence suggest that consistent patient education with prophylactic foot care for those judged to be high risk may reduce foot ulceration and amputations. (Mcinnes et al., 2011) Good foot care depends on initial education about the interaction of all the treatment factors and ongoing support and reinforcement. Education of patients with T2DM is considered a fundamental aspect of diabetes care because, patients are responsible for the day-to-day control of diabetes and its complications. (Haas et al., 2012) Education for patients with T2DM aims to improve their knowledge and skills, enabling them to take control of their own condition and to integrate self-foot care into their daily lives. Several meta-analyses have demonstrated that self-foot care along with aerobic exercises is associated with clinically important benefits in persons with T2DM, such as reductions in glycated hemoglobin (HbA1C) of 0.36% to 0.81% and also reduces the risk for developing foot complications. (Chodosh et al., 2005; Gary et al., 2003; Minet et al., 2010)

5.2.3 Effect of structured foot health program on intrinsic foot muscles and plantar tissues in T2DM

In India, diabetic foot evaluation is the most ignored aspect of diabetes care. Because of social, religious, and economic reasons, people walk barefoot, which could lead
Foot complications in diabetes are common, but it is unclear whether the adjustments are initiated from the skin surface or underneath plantar tissues. Intrinsic foot muscle strength and somatosensory information from the plantar surface of the foot are important elements for safe ambulation and standing balance. (Chao et al., 2011) Therefore, maintaining adequate intrinsic foot muscle strength is really important for the effective execution of natural processes of daily living. (Mickle et al., 2012) Studies documented that subjects with T2DM present with intrinsic foot muscle atrophy, which further develops to deformities like claw toe deformity and hammer toe deformity. (Shashi K., et al 2015; Andersen et al., 2004; Bus et al., 2002; Ledoux et al., 2008; Severinsen et al., 2007; Bus et al., 2002)

Several imaging techniques, such as Conventional Radiography, Computed Tomography, Magnetic Resonance Imaging (MRI), and Ultrasonography were used to study the structural changes in the diabetic foot. Ultrasonography is considered to be a less time-consuming, effective method for the evaluation of the thickness and cross-sectional area (CSA) of soft tissues in subjects with T2DM. (Shashi K., et al 2015; Ranachowska et al., 2010; Severinsen et al., 2007) Therefore, in the present study, we incorporated the Ultrasonography to assess the intrinsic foot muscles. Even though several studies have proved that long-standing T2DM with and without peripheral neuropathy is associated with intrinsic foot muscle atrophy leading to toe deformities, no strategies have been implemented to prevent intrinsic foot muscle atrophy. The possible reason for the intrinsic foot muscle atrophy could include non-enzymatic process of glycosylation, which cause the foot muscle to lose their functional capability to control movements at the joint level. Other potential causes of intrinsic muscle atrophy could be due to cellular and molecular
mechanisms, including apoptosis and abnormality of ubiquitin-proteasome and lysosome systems. (Frier et al., 2008; Sophie et al., 2006)

Therefore in the present study, in addition to aerobic exercise, intrinsic foot muscle strengthening is used as one of the important component to delay the structural changes in the foot. To the best of our knowledge, the present study is the first study to incorporate intrinsic foot muscle strengthening as one of the important component of structured foot health program on Indian T2DM population. In the present study, an increased thickness of Extensor Digitorum Brevis muscle by 0.04cm on right and 0.03cm on left foot, cross-sectional area by 0.32cm² on right and 0.15cm² respectively on experimental group whereas in control group the thickness and cross-sectional area of EDB was reduced in both right and left foot at 12th week was reported. (Table 11) Similarly, 1st lumbrical, 1st Interosseous and adductor hallucis muscles also reported a significant increase in the thickness in experimental whereas in control group we found reduced thickness (Table 11).

*A possible reason for improvement in intrinsic foot muscles thickness:* As a result of strengthening intrinsic foot muscles, a significant increase in the muscle thickness and cross-sectional area was observed in the present study. The possible reason could be due to strengthening exercises lead to increase in myofibril thickness and number. This might have maintained or improved the intrinsic foot muscle strength. Clinically, strengthening exercises are proven to be effective in maintaining or improving the muscle strength through a physiological adaptation. In subjects with T2DM with and without peripheral neuropathy, progressive intrinsic muscle atrophy lead to clawing of toes and anterior translation of plantar fat pad, exposing metatarsals into high plantar pressure. Therefore,
maintaining or improving the intrinsic foot muscle strength can play a major role in preventing toe deformities and abnormal plantar pressures on the metatarsals. Another possible reason include exercise induced glycemic control and reduced neuropathy symptoms. Moderate intensity aerobic exercise and strengthening of intrinsic foot muscle might have caused restoration of peripheral nerve functions by inhibition of aldose reductase (AR) leading to sparing of Nicotinamide Adenine Dinucleotide Phosphate hydroxide (NADPH) which may then participate in the synthesis of nitric oxide which stimulates vasodilatation thereby improving microcirculation to the foot muscles.

**A possible reason for change in plantar skin and fat pad thickness:** In the present study, an increased thickness of plantar skin and fat pad ranged from 0 to 0.03cm on plantar skin and 0.01 to 0.06cm on plantar fat pad respectively at 12th week after the intervention was reported. The possible mechanism could be due to added effect of glycemic control and increased microcirculation caused by aerobic exercises and intrinsic foot muscle strengthening through increased activity of nitric oxide release. In the untrained vessel, basal release of nitric oxide causes subjacent smooth muscle cell vasodilatation which acts to homostatically regulate vessel wall shear. In response to exercise, acute increase in shear stress, associated with repetitive exposure to increase blood flow during bouts of exercise, stimulates increased endothelial nitric oxide production and consequent vasodilatation. This improved microcirculation might have improved the circulation to the nerves which prevented from developing motor neuropathy which indirectly prevented the toes from undergoing to deformity like claw toes and hammer toes. This also prevented the anterior translation of the plantar fat pad maintaining normal cushioning under the metatarsal heads.
5.2.4. Effect of structured foot health program on foot kinetics (Plantar pressures) in T2DM

Kinetics of foot in T2DM is mainly focus to understand the mechanism of plantar pressures on the foot. A large number of factors have been identified as possibly responsible for the increase in plantar pressure in the feet of diabetics. Such factors include an increase in body weight, limitation in joint mobility, the thickness of the plantar tissue, change in tissue mobility, and change in muscle strength, motor/sensory neuropathy, and change in structure/deformity of the feet. Studies documented that plantar pressure in T2DM subjects is greater than in non-diabetic subjects and it is the best predictor of risk for developing foot ulcers. These plantar pressure can be well analyzed using advances plantar pressure analysis devices. (Anjos et al., 2010; Chao et al., 2011; Maiya et al., 2015; Mueller et al., 2003; Viswanathan et al., 2003) F-scan (R2=0.97) (Luo, Berglund, & An, 1998), Novel emed-x (ICC <0.70), Tekscan (ICC 0.44 to 0.95), i-step and win track (ICC 0.75 to 0.90) are the reliable and commonly used devices in analyzing plantar pressures.

Planter pressure devices are capable of analyzing plantar pressures during the static and dynamic mode. The parameter’s which can be obtained are Average plantar pressure, peak plantar pressure, forefoot pressure, hind foot pressure and also the type of foot arch with respect to plantar pressure (Maiya et al., 2015; Syed et al., 2013).

In the present study we have used iStep® scanner (Aetrex Worldwide, Teaneck, NJ, USA) to record plantar pressures under both feet simultaneously. We found increased plantar pressures on both the foot in control group. Average plantar pressure which is defined as actual pressure averaged over the total number of sensors, increased on both feet
by 0.16kg/sensor (p=0.04) on the right and 0.19kg/sensor (p=0.01) on the left feet respectively at the 12th week (Table 9). Studies documented that T2DM subjects present with increased plantar pressures even before the peripheral neuropathy. (Bacarin ., 2009; Maiya et al., 2015; Yu et al.,2008) Neuropathy has been identified as one of the major risk factors for diabetic foot ulceration and amputation. The lack of protective sensation from sensory neuropathy leads to repetitive trauma to an area of high pressure. (Driver et al.,2010) Whereas in the present study also control subjects were with mild peripheral neuropathy, where their MNSI B score 2 at the baseline and at the end of the 12th week the MNSI B score was 3 which denotes mild peripheral neuropathy (Table 8).

A possible reason for reduced plantar pressures: In subjects with long-standing T2DM as the disease progresses, it is associated with adaptive structural alterations caused due to neuromuscular adaptations as a result of sensory neuropathy, motor neuropathy and autonomic peripheral neuropathy. Dryness of plantar skin as a result of autonomic peripheral neuropathy and loss of sensation and intrinsic foot muscle atrophy as a result of peripheral neuropathy is considered to be a the risk factor for increased plantar pressures under the foot. Intrinsic foot muscle atrophy causes instability of the metatarsophalangeal joints and anterior migration and displacement of the fat pad that is normally located directly under the metatarsal heads. (Oh-Yun, 2001) Anterior displacement of the fat pad makes the forefoot more vulnerable to injury from accumulated trauma during walking which further increases the plantar pressures. High plantar pressures may lead to the formation of callus, breakdown of tissue and the formation of ulcers. These lesions often are followed by infection, gangrene, and amputation. Therefore offloading the plantar pressures plays a major role in preventing several complications.
Today, there are several offloading techniques available to reduce the plantar pressures. Casting, molded insoles, rocker shoes, and therapeutic footwear have been used to spread the pressures, prevent the localized pressure on the forefoot, and increase the area of the weight-bearing force. Whereas in the present study, intrinsic foot muscle strengthening along with self-foot care showed a significant reduction in plantar pressures especially on the forefoot. Average plantar pressure reduced by 0.03kg/sensor on the right foot and increased by 0.01kg/sensor on the left foot. Whereas for plantar pressure showed a significant reduction by reducing 0.019kg/sensor on the right forefoot and 0.09kg/sensor on the left forefoot. Similarly, we also observed a reduction of plantar pressure on the hind foot by 0.10kg/sensor on right hind foot and 0.013kg/sensor on the left hind foot at the 12th week (Table 9). Whereas in a study by sartor et al, analyzed kinetic and kinematics of T2DM subjects with ankle foot exercises and gait training for 12 weeks, and found no significant reduction in forefoot plantar pressure and the limitation of this study was the small joint mobility was not assessed which is controlled by intrinsic foot muscles. (Sartor et al., 2012) But in the present study, we analyzed the intrinsic foot muscles changed through musculoskeletal ultrasonography and found a significant reduction of intrinsic foot muscles in control group whereas in experimental group a significant increase in the thickness of intrinsic foot muscles was observed and also reduction in the average plantar pressure especially forefoot plantar pressure followed by exercises and self-foot care..

The possible reason for the reduction in plantar pressure could be due to improved intrinsic foot muscle thickness which was might have achieved through intrinsic foot muscle strengthening which is an important component of structured foot health program.
which helped in redistributing the plantar pressure. Studies documented that, atrophy of intrinsic foot muscles lead to clawing and hammering of the toes which further leads to anterior translation metatarsal fat pad. (Sicco a. Bus et al., 2005; M. E. Fernando et al., 2014b; Kumar et al., 2015). Strengthening of intrinsic foot muscles might have reversed this process by not letting the toe go for clawing or hammer deformity which maintained the fat pad in place protecting the metatarsal heads from high load. This might have maintained the normal shock absorbing effect under the metatarsal heads which reduced the plantar pressures under the metatarsals.

Another possible mechanism could be due to added effect of exercise induced glycemic control and increased peripheral microcirculation caused by aerobic exercises and intrinsic foot muscle strengthening through increased activity of nitric oxide release. In the untrained vessel, basal release of nitric oxide causes subjacent smooth muscle cell vasodilatation which acts to homeostatically regulate vessel wall shear. In response to exercise, an acute increase in shear stress, associated with repetitive exposure to increase blood flow during bouts of exercise, stimulates increased endothelial nitric oxide production and consequent vasodilatation. This maintains the normal functioning of the muscle and skin to regulate the perspiration function. This prevents the skin from dryness and other skin related complications like fissure and callus.

Use of appropriate footwear might have added effect on offloading the forefoot plantar pressure. Several studies have reported that offloading footwear’s play a major role in distributing the plantar pressure. Whereas, in the present study we recommended all the subjects to used offloading footwear’s indoors and outdoors and this might have helped in distributing the plantar pressures and prevented the foot from pressure induced injuries.
5.2.5 Effect of structured foot health program on foot kinematics (Spatiotemporal gait characteristics) in T2DM

Subjects with T2DM are 15 times more likely to report a fall-related injury (fracture, sprained an ankle, cuts and bruises) during standing and walking when compared to people without T2DM. In addition, peripheral neuropathy is a risk factor for developing plantar ulcers. Most of these ulcers are thought to develop during walking. (J.K., Richardson et al., 2002)

Normal walking requires sensory inputs to modify learned motor patterns and muscular output to execute the desired action. An intact central and peripheral nervous system to initiate and control the movement, adequate muscle strength, bones and joints moving in the full range are the necessities for normal locomotion which is the most natural daily activity for humans. (G Yavuzer et al., 2006) Gait analysis studies for subjects with T2DM vary on their inclusion criteria, the definition of neuropathy, walking surface, data collection methods, and analysis technologies. Results from these studies can be confusing or contradictory. However, two clear trends emerge: decreased walking speed (velocity) and an increased base of gait (step width measured from one heel to the other perpendicular to the line of progression). If the T2DM subjects walk with both decreased speed and an increased base of gait, these gait characteristics should serve as red flag warnings for advancing neuropathy and foot ulcer risk (Brach et al., 2008; J. Petrofsky et al., 2005; Sari Goldman et al., 2011).

Researchers have also reported additional gait parameters in subjects with T2DM. These include decreases in cadence, step length, single limb support time, plantar flexion
moments, step variability, and knee and ankle mobility. Also, there are increase in double limb support time and the gait cycle duration. Furthermore, patients with diabetes may walk even slower on irregular surfaces like cobblestones. However, one should keep in mind that most of these additional parameters could be secondary to slower walking speeds. Slower walking speeds are associated with increased plantar pressures, decreased joint angles, decreased single limb support and increased double limb support time (L. Allet et al., 2008; Lara Allet et al., 2009; Raspovic, 2013; Wrobel & Najafi, 2010).

In the present study, we analyzed spatiotemporal gait parameters which include step duration, swing duration, step length, gait cycle duration and double stance duration using Win-Track (Medicapteurs Technology. France) which has a reliability of 0.75 to 0.90. Step duration is defined as time spent during one single step (800ms). Swing duration is defined as the time while the foot is not in contact with the floor (400ms). Step length is defined as the distance between two lines cutting feet equal halves (80mm ± 35mm = 100 – 150mm). Gait cycle duration is defined as the time interval between the successive instant of foot floor contact of the same foot. Double stance duration is defined as time while both the foot in contact with the floor which is approximately 20% of the gait cycle.

In the present study, the control group reported an increase in step duration by 25ms, swing duration by 35ms, gait cycle duration by 125ms and double stance duration by 65ms whereas step length was reduced by 8mm which indicates the worsening of gait characteristics in control group. In the experimental group, a significant reduction of swing duration by 730ms which is very high than MCD 40ms and double stance duration by 761ms which is also higher than MCD 40ms. whereas, step length was increased by 51mm
(MCD 20ms) which indicates a significant improvement in the spatiotemporal characteristics in the experimental group. Whereas, in the experimental group, a significant improvement in gait characteristics was reported. There was a significant reduction of swing duration by 730ms, gait cycle duration by 135ms, and double stance duration by 761ms. Step length increased by 51mm at 12th week after the intervention (Table 10). Although there are evidence that an exercise regimen improves clinical measures of balance in patients with peripheral neuropathy, (Richardson et al., 2001) clinical trials investigating the gait of diabetic individuals generally focus on increased foot pressure and related to the high risk of ulcers in such patients. (Pataky & Vischer, 2007) Only a few studies have evaluated treatments that aim to improve gait and prevent complication risk. (Morrison et al., 2014; Perrochon et al., 2015; J. Petrofsky et al., 2005; J K Richardson et al., 2001; J K Richardson et al., 2004)

A possible reason for improved spatiotemporal gait parameters: It is well documented that subjects with long-standing T2DM are associated with impairment in the gait and increased the risk for foot complications may have a detrimental influence on their physical activity level. Diabetic patients with inadequate gait stability or who experience a foot related complications may not be able to meet the exercise prescription recommendations. Their risk of diabetic complications and decreased musculoskeletal function, therefore, increase with further negative consequences for physical activity. Therefore, in the present study, we developed a structured foot health program which consists of aerobic training, intrinsic foot muscle strengthening, and self-foot care.
Steven et al. tested an insulin sensitizer, rosiglitazone, which promises to reverse some of the circulatory impairments are seen in diabetes, thereby improving patients’ gait. They reported encouraging results after administering rosiglitazone (decreased step width, reduced reaction time and less acceleration at the joints). However, rosiglitazone was recently associated with increased risk of myocardial infarction and death from cardiovascular incidents. (Steven E Nissen et al., 2007) Richardson et al., evaluating patients with a various form of peripheral neuropathy (30 of 42 of whom had diabetic peripheral neuropathy), found that the use of a cane, ankle orthoses or touching a wall improved step-width range, step-time variability, and speed while walking under challenging conditions. (James K. Richardson et al., 2004)

Tsang et al. and Orr et al. have investigated the effect of a specific physical training program not only on the activity level and quality of life of diabetic patients but also on their habitual and maximal walking speed. However, both studies seem to have evaluated the same group of participants. In these studies, the effect of a ‘Tai Chi for Diabetes’ program (twice a week for 16 weeks) on gait, balance, musculoskeletal and cardiovascular fitness, self-reported activity and quality of life was compared with that of sham exercises. Gait speed and balance improved, but no significant differences between groups were reported. (Orr et al., 2006; Tsang et al., Orr et al., 2007) whereas in the present study, we observed a significant difference in swing duration, step length, gait cycle duration and double stance duration between the groups.

The possible reason for improvement in the spatiotemporal gait parameters could be due to glycemic control by 9.20% at baseline which reduced to 8.25% at the 12th week
after the intervention (Table 8). Glycemic control play a major role in preventing diabetic peripheral neuropathy. Several exercise-induced vascular and metabolic changes could be invoked to explain the effects of training on DPN development. Human and experimental studies suggest that exercise stimulates endothelium-dependent vasodilatation through NO synthesis. Higher vascular endothelial growth factor (VEGF) expression during short-term exercise has been proposed to play a role in endoneurial blood flow increase. This could improve the osmoregularity of the cells thereby maintaining or improving never function.

Another possible reason for improve gait parameters could be due to strengthening of intrinsic foot muscles which maintained the intrinsic foot muscle strength which prevented the toes from undergoing deformed and maintained the plantar fat pad in place. Strengthening also improve abnormal perfusion and plasma viscosity facilitating oxygen delivery. (Gustafsson et al., 2011) Exercise also improve abnormal perfusion and plasma viscosity facilitating oxygen delivery. (Chmetterer et al., 2002) It is known that exercise training exposes the vessels to repeated episodes of hyperemia. The elevated shear stress from the increased blood flow of aerobic exercise augments vasodilatation over the long term by increasing the vascular expression of nitric oxide synthase and by enhancing the release of nitric oxide. (Fukai et al., 2000; A. Maiorana et al., 2003) The increase of nitric oxide synthesis or bioavailability may be useful in preventing diabetes-induced changes in the polyol pathway. (Ramana et al., 2003) Exercise-induced nerve function changes could be also related to an improvement of Na/K ATPase activity. In fact, training has been reported to increase the concentration of Na/K-ATPase in rat muscle cells. In addition, K (ATP) channel openers have been shown to provide marked beneficial effects on nerve perfusion and function in experimental diabetic neuropathy. (Hohman et al., 2000)
5.2.6 Effect of structured foot health program on quality of life in T2DM

The quality of life is important for people with diabetes and their healthcare providers for several reasons. This is because many people who suffer from diabetes and who have a poor quality of life, often have less attention to their self-care and disease management. When self-care is diminished in diabetes, it leads to poor glycemic control and increase the risk of complications. Thus, quality of life issues is crucially important because they may powerfully predict an individual’s capacity to manage his disease and maintain long-term health and wellbeing. (Price, 2004)

The World Health Organization (WHO) defines Quality Of Life (QOL) as an individual’s Perception of their position in life in the context of the culture and value systems in which they live and in relation to their goals, expectations, standards, and concern. (WHO 1998) It is a broad ranging concept affected in a complex way by the person’s physical health, psychological state, the level of independence, social relationships, personal beliefs and their relationship to salient features of their environment. (Skevington et al., 2004)

T2DM and its foot complications are usually progressive in nature leading to poor quality of life. As discussed before, peripheral neuropathy is considered to be the most common complication of T2DM followed by other foot complications. Due to the involvement of several pathway mechanisms foot complications develop. Abnormal perfusion and plasma viscosity facilitating oxygen delivery, nitric oxide synthesis making more reliability on polyol pathway which further alters Na/K ATPase activity leading to diabetic foot complications. (Chmetterer et al., 2002; Fukai et al., 2000; Gustafsson et al.,
In the present study, we postulated that structured foot health program which consists of moderate intensity aerobic exercise, intrinsic foot muscle strengthening, self-foot care can play a vitally important role in modifying the progression of foot complications thereby modulating the quality of life.

Many studies have used various instruments to assess health-related quality of life issues associated with diabetes and its complications. Whereas in the present study, we have used WHOQOL-BREF questionnaire. The questionnaire consists of 26 items: two individual items that evaluate the overall quality of life and satisfaction with health, and 24 items clustered into four domains (physical health, perception, social relations, and environment). The range of the scale for individual items is 1 -5, while the score in domains is on a scale of 4-20 and converted to a scale of 0-100 using transformed scoring. Higher the score indicates better the quality of life.

In the present study, the experimental group had more scores of WHOQOL-BREF in all the domains (physical health, psychological, social relationships, environment) depicting an improvement in the quality of life of T2DM subjects. Whereas in control group physical health and psychological domain scores were reduced at the 12th week indicating worsening in quality of life (Table 14). Emphatic effects of exercise on psychometric and physical measures have been reported previously in T2DM. (Chyun et al., 2006; Eljedi et al.,2006; Fal et al., 2011; Ovayolu et al., 2008; Srinivas et al.,2014; Sukala et al., 2013; Zeleníková et al.,2014) A study comparing group rehabilitation with individually tailored sessions found that patients who underwent individual sessions showed better improvement in episodes of hypoglycemia and hyperglycemia as compared
to patients undergoing group rehabilitation. (Vadstrup et al., 2011) It is quite evident from the present study that individually tailored structured foot health program not only results in amended physiological measures in T2DM but also results in enhancement of measures of WHOQOL-BREF. Whereas for the control group, standard care alone did not result in enhancement of WHOQOL-BREF, as in the control group lower scores for physical health and psychological domain of WHOQOL-BREF signify a greater disability. A possible reason could be that standard care alone is unable to cause modulation toward healthy lifestyle in due time.

It is very important to understand the effect of intensive glycemic control (multiple injections of insulin) on the quality of life which still remains to be researched, as there is a lack of evidence supporting the fact that intensive drug or insulin therapy has acute or chronic benefits. A study examining the possible role of physical activity in older adults found that a decrease in physical activity negatively impacts the health-related quality of life in diabetes. (Vadstrup et al., 2011) Moreover, it has been documented that lower level of physical activity is associated with poor health-related quality of life. Lower physical and mental health-related quality of life may be an independent indicator of increased cardiovascular-related mortality risks in T2DM. (Landman, 2010) The Even low threshold of physical activity in patients with T2DM has the potential to cause appreciable changes in metabolic risk factors in T2DM. A home-based walking (low threshold) is also reported to have a better metabolic control and can be advised for the patient population as it might also help in improving the health-related quality of life.
Ashford et al investigated the physical life of people with diabetes who presented with foot ulceration through semi-structured interviews using a phenomenological approach. It was found that footwear was a major factor, in that many people disliked the type of shoes that they were required to wear. This study highlighted how females felt that their femininity was undermined by therapeutic footwear. However, this study assessed only a relatively small sample size and there was an uneven distribution of males (n = 15) and females (n = 6); Therefore, the results may not be as accurate in proving that footwear is a real issue compared with those from larger scale studies. Whereas even in the present study also male and female ratio (100:16) was uneven even though the sample size was high.

A study by Dixit et al looked at the impact of aerobic exercise on quality of life in people with type 2 diabetes who suffer from peripheral neuropathy. Participants completed a moderate-intensity aerobic exercise program for eight weeks. The study found that the group who exercised saw significant positive changes in their reported neuropathic pain, activities of daily living, impact on social relationships, and quality of life compared to the non-exercise group. These results highlight the importance of physical exercise in improving both symptoms and quality of life for people with T2DM. Authors also documented that, they screened 347 patients out of which 335 cleared the eligibility criteria, but still only 87 patients gave their consent to participate in the trial and observed a large number of dropouts in both the groups. Authors stated that reason for dropouts could be due to poor awareness and education regarding diabetic peripheral neuropathy in the region. Previously, poor awareness regarding diabetic foot awareness and self-management has been documented by the researchers in India. (Dixit et al., 2011; Dixit et
al., 2014) This factor was considered in the present study and developed a structured foot care program which includes exercise protocol, self-foot care, and foot health education which showed a significant improvement in quality of life in subjects with T2DM
5.2.7 Summary of Discussion

Phase-I:

In the present study high prevalence of musculoskeletal and foot complications was reported in T2DM subjects, the possible reason could be due to neuropathic, vascular, and immune system components, which all show a base relationship with the hyperglycemic state of diabetes. Hyperglycemia produces oxidative stress on nerve cells and leads to neuropathy, Nonenzymatic glycosylation of proteins resulting in AGE formation and connective tissue stiffening, nerve damage (Neuropathy), vascular damage (blood vessel), hyperuricaemia, reduced bone density, low-grade chronic inflammation and abnormal levels of insulin and insulin-like growth hormone.

Another possible reason for increase in the prevalence of musculoskeletal and foot complications could be due to lack of awareness and education regarding diabetes, its complications and self-care.

Phase-II:

In the present study, we found significant improvement in biochemical characteristics, foot biomechanics (temporospatial gait parameters), intrinsic foot muscles and quality of life in subjects in experimental group who received structured foot health program as compared to standard therapy alone. Therefore, it is clear from the present study that structured exercise program plays a vitally important role in subjects with T2DM and foot complications. A structured foot health program which emphasize on physical activity combined with self-foot care and foot health education plays major benefits as compared to standard therapy alone.