CHAPTER 2

REVIEW OF LITERATURE

SECTION 1

2.1 Search methods for identification of studies

We searched PubMed, MEDLINE, web of sciences, EMBASE, science direct, Scopus CINAHL and web of science (2000 till date) for cross-sectional, RCTs, cohorts and case-control studies in English language only, using the following search terms: Type 2 diabetes mellitus, peripheral neuropathy (diabetic polyneuropathy or peripheral nervous system diseases, distal symmetrical polyneuropathy, painful neuropathy), Foot complications (skin manifestations, callus, bunions, fissures, claw toes, hammer toes, intrinsic foot muscle atrophy/wasting, ulcers and musculoskeletal complications (shoulder adhesive capsulitis, low back pain, carpal tunnel syndrome, flexor tenosynovitis, Deputryens contracture, plantar fasciitis, muscle fatigue), enhanced glycemic control, foot health program, foot care, aerobic exercise, lifestyle modifications, diet and quality of life in diabetes.

2.2 Need for the review

The prevalence of diabetes has risen dramatically in Westernized societies, in developing countries, and in Asia. (Mohan, Sandeep, Deepa, Shah, & Varghese, 2007). In 2014 there were 415 million people with DM, and this is expected to rise to 642 million by 2040. (IDF 2015) The majority of the 382 million people with DM are aged between 40 and 59, and 80% of them live in low- and middle-income countries. International Diabetes Federation (IDF 2015) reported China as the first country with the highest diabetes prevalence among the top 10 countries with India holding the second position. (IDF 2015). Diabetes is associated with microvascular and macrovascular complications where
musculoskeletal and foot complications are considered to be more common and not given much importance (Dixit S & Maiya A 2014). As the prevalence of foot and musculoskeletal complications increase this puts a burden on the need for appropriate management and care. In India, the foot is the most ignored part of diabetes evaluation. Therefore, review focuses on the prevalence of foot and musculoskeletal complications and to understand the data available on the strategies used for preventing foot complications.

2.3 Study selection process and criteria

A total of 27,465 records were identified using the above-mentioned search engines followed by the filtering the articles for duplication. Based on the title and abstract, 366 records (including cross sectional, RCT, NonRCTs) were included in the review.
SECTION 2

2.4. Diabetes mellitus

Definition

The term ‘diabetes’ was first defined by Araetaeus of Cappadocia (81-133AD) and Mellitus (honey sweet) was added by Thomas Willis (Britain) in 1675 when he detected sweetness in urine. It is said that it was first noticed by the ancient Indians; Shushrutha had named it as ‘Madhumeha’. (Ahmed et al., 2002) After several types of research on diabetes mellitus, it is defined as a group of metabolic diseases characterized by hyperglycemia which results from defects in insulin secretion, insulin action, or both. (ADA, 2010)

Diabetes mellitus (DM) is classified into four categories, type 1 diabetes mellitus (T1DM), type 2 diabetes mellitus (T2DM), gestational diabetes and other forms of DM. (Diabetes, 2010) T2DM is the most common form of diabetes affecting 85-90% of the diabetic population. (IDF 2015) It is a multi-system disease characterized by persistent hyperglycemia caused due to a progressive defect in insulin secretion on the background of insulin resistance. (Guariguata et al., 2014)

2.5 Etiological classification of DM

2.5.1 Type 1 diabetes mellitus (T1DM)

- T1DM results from the autoimmune destruction of the insulin-producing beta cells in the pancreas
- Immune-mediated: there is infiltration of the islets of Langerhans with mononuclear cells containing activated macrophages, lymphocytes, natural killer cells and B lymphocytes.
• β-Cell specificity of the destructive process, with the glucagon and other hormone secreting cells remaining intact.

• Idiopathic

2.5.2 Type 2 diabetes mellitus (T2DM)

• T2DM is a more complex condition with a combination of resistance to the action of insulin in the liver and muscle together with impaired pancreatic β-Cell function leading to ‘relative’ insulin deficiency (Diabetes, 2010).

2.5.3 Gestational diabetes

• Gestational diabetes is defined as the diabetes recognition during pregnancy. The action of placental hormones, reduces the insulin sensitivity and affects glucose tolerance during normal pregnancy. Inability to secrete insulin by islets of pancreas genetically predisposes the women to develop DM (Diabetes, 2010).

2.5.4 Other specific types

• Genetic defect of insulin action (e.g. leprechaunism, lipodystrophies)

• Pancreatic disease (e.g. pancreatitis, pancreatectomy, neoplastic disease, cystic fibrosis, hemochromatosis, fibro calculus pancreata pathy)

• Genetic defect of β-Cell function

• Excess production of hormonal antagonists of insulin (e.g. Growth hormone-acromegaly; glucocorticoids-Cushing’s syndrome; glucagon-glucagonoma)

• Drug-induced (e.g. corticosteroids, thiazide diuretic, phenytoin)

• Associated with genetic syndromes (e.g. Down’s syndrome, Turner’s syndrome)

• Viral infections (e.g. congenital rubella, mumps, Coxsackie virus B)
• Uncommon forms of immune-mediated diabetes (Diabetes, 2010)

2.6 Criteria for the diagnosis of DM (ADA, 2014)

• Glycated hemoglobin (HbA1C) ≥ 6.5%.
• OR Fasting blood sugar (FBS) ≥ 126 mg/dL (7.0 mmol/L) OR
  2-h Post prandial blood sugar (PPBS) ≥ 200 mg/dL (11.1 mmol/L)
• OR a random plasma glucose ≥ 200 mg/dL (11.1 mmol/L).

T2DM in its earliest stages remains asymptomatic, therefore, many cases remain undiagnosed for a long time (Valdez et al., 2009). But, a high proportion of people having diabetes mellitus are undetected globally and especially in developing countries (Beagley et al., 2014). DM will not be diagnosed on time at the earliest in most of the population, it will be diagnosed only during the visit to health care centers due to complications caused by diabetes mellitus or any other health-related problems. Timely diagnosis of DM can prevent patients from receiving adequate intensified treatment in time and predisposes them to the development of diabetic complications.
2.7 Epidemiology of DM

Over the past three decades, the number of people with DM has more than doubled globally, making it one of the most important public health challenges to all nations. The causes of the epidemic of T2DM are embedded in a very complex group of genetic and epigenetic systems interacting within an equally complex societal framework that determines behavior and environmental influences.

2.7.1 Global prevalence of DM

The global increase in the prevalence of diabetes is due to increased population, aging, urbanization and reduced physical inactivity. (Maharaja et al., 2014) The prevalence of diabetes has risen dramatically in Westernized societies, in developing countries, and in Asia. (Mohan et al., 2007). In 2015 there were 415 million people with DM, and this is expected to rise to 642 million by 2040. (IDF 2015) The majority of the 382 million people with DM are aged between 40 and 59 and 80% of them live in low- and middle-income countries.

2.7.2 National prevalence of DM

In 2000, it was reported that India was the “capital for diabetes mellitus” with 31.7 million people with DM followed by China (20.8 million) in second and the United States (17.7 million) third place respectively. (Kaveeshwar et al., 2014). A Recent update by the International Diabetes Federation (IDF 2015) estimates the total number of people in India with diabetes in 2015 was around 69.2 million and this is expected to increase to 123.5 million by 2040 (IDF 2015).
Studies comparing urban India with rural India documented that urban population in India has the highest incidence of T2DM as compared to the rural population. The prevalence of T2DM in rural populations is one-fourth that of the urban population of India and other Indian subcontinent countries such as Bangladesh, Nepal, Bhutan, and Sri Lanka. In a large community survey conducted by the Indian Council of Medical Research (ICMR) in 2011 revealed that a lower proportion of the population is affected in states like Chandigarh 0.12 million, Jharkhand 0.96 million as compared to Maharashtra 9.2 million and Tamil Nadu 4.8 million (Anjana et al., 2011).

The National Urban Survey conducted across the metropolitan cities of India reported a similar trend: 11.7% in Kolkata, 6.1% cent in Kashmir, 11.6% in New Delhi and 9.3% in West India compared with 13.5% in Chennai, 16.6% in Hyderabad and 12.4% in Bangalore (Ramachandran et al., 2015).

As the prevalence of DM in India is drastically increasing, this superimposes the need to develop national policies for the management of T2DM and its complications. In an analysis of preventive measures by Narayan et al on global prevention and control of T2DM stated to include preventive measures in a clinical scenario for the management of T2DM and its complications. The authors further laid emphasis on early recognition of prediabetes and undetected diabetes for implementing effective measures on management of T2DM and its complications (Narayan et al 2012). Our focused national policies that are devised in the interest of T2DM population should have a cumulative effect at the national level to support people with diabetes and also provide them the armamentarium for the control of diabetes. Narayan et al further suggest the development of “cluster visits” with a
multidisciplinary team of health care providers, for people with DM. Moreover, they had further emphasized that people with isolated prediabetes or DM can be referred for lifestyle interventions and follow-up. These focused policies will not only lead to risk reduction associated with DM and other non-communicable disease but will also bring down the prevalence of diabetes and its complications in India which expected to rise to 123.5 million subjects with DM in 2040.
SECTION 4

2.8 Pathophysiology of T2DM

T2DM is a metabolic disorder characterized by insulin resistance and/or abnormal insulin secretion from pancreas β-cells, each of which may predominate and precede the onset of clinical T2DM by many years.

Impaired insulin secretion: Beta-cells of the pancreatic islets of Langerhans release insulin in response to changes in blood glucose concentration. The process is initiated by the transport of glucose into the beta-cells through diffusion facilitated by Glucose transporter 2 (GLUT2). In the beta-cell, glucose is metabolized to generate Adenosine triphosphate (ATP), the central energy molecule, and the ATP/ADP ratio increases. This induces the closure of cell-surface ATP-sensitive potassium (K+) channels and leads to the depolarization of the cell-membrane. Then transmembrane voltage-dependent calcium (Ca2+) channels are opened due to depolarization, facilitating the influx of extracellular Ca2+ into the beta-cell. Finally, a rise in free cytosolic Ca2+ triggers the exocytosis of insulin and decreased early-phase secretion and the advancement of the deterioration of pancreatic β cell function subsequently causes permanent elevation of blood glucose (Féry & Paquot, 2010).
Insulin release from pancreatic cells occurs in a biphasic manner in response to increasing in blood glucose levels. In the first stage, which is a very short acting increase in insulin secretion is accompanied by more slowly evolving the second phase, which endures as long as blood glucose level is raised. On the other hand, a slow increase in plasma glucose level induces a larger secretion of insulin without the first phase (Henquin, Ishiyama, Nenquin, Ravier, & Jonas, 2002).

In T2DM, impairment in both first and second phase is seen and due to this impairment, insulin release occurs early in the natural history of DM, and blunted first-phase insulin release can be demonstrated even in normal glycemic first-degree relatives of T2DM. Furthermore, beta-cell function deteriorates over the years following the diagnosis of T2DM (Radhakrishnan et al., 2014).
Insulin resistance: The main insulin-sensitive tissues in the body are skeletal muscle (accounting for 60-70% of the whole-body glucose uptake), liver (30%) and adipose tissue (10%). Insulin resistance can be determined by the inability of these tissues to react properly to normal circulating concentrations of insulin. To maintain blood glucose levels, the pancreas compensates by secreting more amounts of insulin. After a period of compensating insulin resistance, prediabetes or diabetes usually develops, especially in coexistence with impaired beta-cell function. An early appearance of insulin resistance in the natural history of diabetes was demonstrated by voyage et al., who found that young, healthy offspring of diabetic parents commonly exhibit insulin resistance and impaired skeletal muscle insulin signaling many decades before the onset of overt T2DM (Stancáková, et al., 2002).

Although the mechanisms resulting in insulin resistance are largely unknown, multiple abnormalities in the insulin signaling pathway have been identified. The most important sites are IRS (-1 and -2), PI3K and PKB. Mutations in the IRS1 gene in humans are associated with insulin resistance, and IRS-2 knockout mice show insulin resistance in muscle, fat, and liver, and develop diabetes resulting from the beta-cell failure. (Previs et al., 2000) Several environmental and lifestyle factors also affect insulin sensitivity such as nutritional factors in utero, diet, physical activity, smoking, drugs, and particularly obesity. Obesity, and especially visceral adiposity is strongly associated with insulin resistance and T2DM (Steyn et al., 2004).
SECTION 5

2.9 Complications of T2DM

T2DM is a metabolic disorder that is strongly associated with both microvascular and macrovascular complications resulting in tissue and organ damage in approximately one third to one-half of people with DM.

Microvascular complications include retinopathy, nephropathy and neuropathy, whereas, macrovascular complications include ischemic heart disease, peripheral vascular disease, and cerebrovascular disease. An algorithm based guidelines for screening and treatment of cardiovascular diseases, retinopathy are well developed. But complications like musculoskeletal and foot complications are underdiagnosed and not given much importance at the early stage of T2DM.

2.9.1 Musculoskeletal complications of T2DM

Musculoskeletal complications are the most common microvascular complications seen in T2DM which affects the patient’s quality of life in several ways. These complications are generally not recognized in the early course of the disorder and not treated as compared to other complications of T2DM like peripheral neuropathy, nephropathy, retinopathy, and cardiomyopathy. Musculoskeletal complications are considered to be some of the causes of disabilities which involve not only the joints but also the bones and soft tissues of the body. (Attar, 2012) Musculoskeletal complications are always associated with inflammatory conditions affecting the bones (diffuse idiopathic skeletal hyperostosis), ligaments, muscles (muscle infarction), tendons (flexor tenosynovitis, Dupuytren’s disease), peripheral nerves (neuropathy, carpal tunnel syndrome), and blood vessels (Vasculopathy) (Fauci et al., 2008).
2.9.1.1 Adhesive capsulitis

T2DM can affect the shoulder in several ways. First, shoulder adhesive capsulitis or frozen shoulder is a rheumatological condition, has been reported in 10-29% of the T2DM population as compared with 3–5 % in non-diabetic subjects. (P. E. Arkkila et al 1996) It is characterized by progressive restriction of shoulder movements especially shoulder abduction and external rotation. The frequency of shoulder adhesive capsulitis in the T2DM population is 5 fold risk more than the normal population (Lebiedz-Odrobina et al., 2010) and it is associated with the duration of diabetes and age.(Gauri et al., 2009) Most patients with frozen shoulder (82%) have a duration of T2DM more than 5 years, and as the duration of diabetes becomes longer, the incidence of frozen shoulder becomes more (Kindy et al., 2010).

Connie et al. in 2008 studied the prevalence of a T2DM and adhesive capsulitis of the shoulder which revealed that subjects presenting with adhesive capsulitis had a 71.5 % chance of having a T2DM (38.6 % chance of being diabetic and a 32.95 % chance of being prediabetic)(Tighe et al., 2008) It was also found that Bilateral involvement is more frequent in subjects with T2DM than in nondiabetic subjects (33 to 42 % vs. 5 to 20 %) (Crispin et al., 2003). Shoulder adhesive capsulitis is found to be associated with other diabetic complications such as limited joint mobility, autonomic neuropathy with T2DM. The exact mechanism is unknown, but it is thought that excessive glucose concentration in diabetic patients can lead to a faster rate of collagen glycosylation and crosslinking in the shoulder capsule, restricting shoulder range of motion.(Hsu et al., 2011)
2.9.1.2 Reflex sympathetic dystrophy

It is also known as “shoulder-hand syndrome” and it may be associated with adhesive capsulitis. Subjects may complain about pain from the shoulder to hand in the affected limb. Classical examination findings include swelling of the affected limb, shiny appearance of skin and change in temperature, insensitivity to temperature and touch and vasomotor instability. (Al-Homood et al., 2013)

2.9.1.3 Stiff hand syndrome/Cheiroarthropathy/limited joint motion

Diabetic stiff hand syndrome or Cheiroarthropathy is the most studied form of limited joint mobility syndrome that affects the extremity. Typically, it begins as cutaneous changes around the metacarpophalangeal and proximal interphalangeal joints of the fifth finger and progresses to all the fingers. (Lebiedz-Odrobina et al., 2010) The prevalence of stiff hand syndrome varies from 38% to 58% of T1DM subjects and from 45% to 76% of T2DM subjects. Patients can be asymptomatic or complain of pain, which increases with the use of the extremity or from paresthesia. (Silva & Skare, 2012)(Lebiedz-Odrobina et al., 2010, Pandey et al., 2013). It was also found that the prevalence of stiff hand syndrome increases with the duration of T2DM and is associated with PN. (Pandey et al., 2013) The stiff hand syndrome is diagnosed based on its characteristic findings and physical examination. The subject’s inability to join their palms together completely without a gap between opposed palms and fingers is known as “prayer sign”. (Lebiedz-Odrobina et al., 2010) Stiff hand syndrome is considered to be influenced by poor glycemic control, although the association between musculoskeletal complications and glycemic control remains controversial.
2.9.1.4 Duputryens contracture

Dupuytren's contracture results from a thickening, shortening, and fibrosis of the palmar fascia. Nodule formation along the fascia is seen. Flexion contractures of the fingers may result, usually at the fourth finger, but sometimes involving any of the second through fifth digits. (Lebiedz-Odrobina et al., 2010, Loos et al 2007) Various studies have reported an incidence of 21-63% duputreyns contracture in T2DM in the contract of 5-22% of the non-diabetic population. But in a study conducted by Sarkar RN observed the incidence of 46.9%, out of which 84% were of T1DM subjects. (Sarkar RN et al., 2003) The diagnosis of Deputryens contracture is clinical based on the history of painless loss of extension of the fingers and palpable discrete nodules along the course of the flexor tendons near the distal palmar crease. (Abe et al., 2004)

2.9.1.5 Carpel tunnel syndrome

Carpal tunnel syndrome (CTS) is a clinical condition caused by compression of the median nerve beneath the transverse carpal ligament. The syndrome is characterized by pain and paresthesia in the territory from the thumb to the middle portion of the fourth finger which worsens during the night and can radiate to the forearm. (Burt et al., 2011, P. E. T. Arkkila et al., 2003) The prevalence of CTS in T2DM was found to be between 11-25% being more common in women (Papanas et al., 2010, Ebrahimzadeh MH et al., 2013, Pandey et al., 2013) In advanced cases atrophy of the thenar muscles and grip strength loss can be seen. However, some authors believe that the real predisposing factor to carpal tunnel syndrome is obesity common in patients with T2DM. (Geoghegan et al., 2004) A study of 791 patients with carpal tunnel syndrome referred for the electrophysiological study has shown that a diagnosis of DM, female sex, obesity and age between 41 and 60 years were risk factors for carpal tunnel syndrome. (Becker et al., 2002)
Carpal tunnel syndrome is usually diagnosed based on history and clinical findings. Classically, subjects complain of burning, paresthesias, or sensory loss along the median nerve distribution. They may also complain of pain in the same area often with radiation proximally into forearm and arm. Tinel’s sign (tapping over the median nerve on the volar aspect of the wrist) may be useful in diagnosis but is not usually positive. A positive Tinel’s sign produces paresthesias distally in the hand. Phalen’s test (the wrist flexion test) may also assist in diagnosis. But like Tinel’s sign it is somewhat variable. In Phalen’s test subjects are asked to flex both wrists so that the dorsum of both the hands are touching and to hold that position for 60 seconds. A positive Phalen’s test consists of paresthesias being reproduced in the hand with this maneuver. Electromyography/nerve conduction velocity testing can confirm the diagnosis of carpal tunnel syndrome in uncertain cases and can also help to localize the site of nerve entrapment. (Kim et al., 2001)

2.9.1.6 Trigger finger/ flexor tenosynovitis

Flexor tenosynovitis presents typically as fingers locked in flexion, extension or both, more commonly involving the thumb, the third finger and/or the fourth finger. (Lebiedz-Odrobina et al., 2010) It results from fibrosis with tendon thickening as it passes through the pulley or one bone prominence, limiting its motion inside the sheath. A volume increase distal to the constriction point causes pain and difficulty in flexing and extending the corresponding finger, which might become locked. (P. E. T. Arkkila et al., 2003) The prevalence of trigger finger in patients with DM ranges from 5% to 36% in those with T1DM or T2DM as compared with 2% in non-diabetic subjects and (Cagliero et al., 2002) its development being associated with longer disease duration. When compared with non-diabetic subjects, those with DM have a tendency to the simultaneous
involved in more than one finger. (Kameyama et al., 2009) According to Koh et al. the involvement of three or more fingers is highly suggestive of the association with T2DM and also found that “the incidence of trigger digits was about four times higher than in the non-diabetic population (Koh et al., 2010) 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 et al., 2008)

2.9.1.7 Low back pain

Low Back Pain is a pain or discomfort localized on the low back in the lumbar region with or without radiating pain (Woolf et al., 2012). It is the most common musculoskeletal disorder in developing countries and is considered to be a leading cause of work-related disability. (Storheim et al., 2014, Van Tulder et al., 2002) Low back pain is classified into acute, sub-acute chronic and recurrent based on the duration and recurrence.(Woolf et al., 2012) The evidence is emerging on the association between musculoskeletal manifestations including low back pain and some attributes of T2DM such as hyperglycemia, neuropathy, reduced muscle strength, flexibility and increased adiposity (Eivazi et al., 2012).

Although the exact mechanism of low back pain in T2DM is not well defined it is found that the prevalence is high. In a study conducted by O.A. Idowu in 2015 documented a prevalence of 46.2% (Idowu et al., 2015) in T2DM subjects, 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). Even though the prevalence of low back pain in T2DM is found to be high, most of the studies concentrated more towards the extremities where the low back pain is mostly ignored.

### 2.9.1.8 Muscle fatigue

Subjects with T2DM suffer from serious health problems that relate to physical, mental and social aspects of their lives. (Fritschi et al., 2010) Fatigue, a common symptom among diabetic patients may be the direct result of physiological processes, treatment, and complications associated with long-term DM. According to previous studies, up to 60% of patients with DM experience fatigue symptoms (Drivsholm et al., 2005; Fritschi et al., 2010).

Overweight and engaging in low levels of habitual physical activity have been strongly associated with fatigue and have special clinical relevance for many subjects with T2DM. The physiological and psychological phenomena that mediate the relationship between obesity and fatigue have not been fully elucidated; however, There is a growing body of literature suggesting that increased levels of pro-inflammatory cytokines may be significant factors in fatigue levels. (Miller et al., 2007) There is a growing interest in the relationship between self-reported feelings of fatigue and physical activity. Much evidence supports the positive effects of regular physical activity on alleviating symptoms of fatigue. (Puetz et al., 2006) Regular physical activity, especially vigorous physical activity, has been shown to improve aerobic capacity and muscle mass, enhance metabolic substrate use for energy. It has been noted that individuals with diabetes engage in low levels of physical activity, which may lead to reductions in aerobic capacity. (Lim et al., 2005)
2.9.2 Foot complications of T2DM

T2DM is associated with microvascular and macrovascular complications where foot complications followed by diabetic peripheral neuropathy (DPN) and peripheral vasculopathies are considered to be the most common complication with a higher prevalence of 52% among T2DM subjects. Other foot complications include Peripheral neuropathy, calluses, fissures, in-growing nails, hammer toes, bunions, fungal infection and ulcers.

2.9.2.1 Diabetic peripheral neuropathy (DPN)

DPN is the most common complications of long-standing T2DM. It affects somatic sensory, motor nerves and autonomic nerves. The prevalence of DPN ranges from 7% in subjects within 1 year of T2DM duration and 50% in subjects with duration of T2DM more than 25 years (Yagihashi et al., 2011).

Distal and sensory predominant nerve fiber degeneration, axonal loss and endoneurial microangiopathy are the characteristic findings in DPN. (Tsitouras et al., 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. Some 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 microangiopathy changes of endoneurial microvessels later, developed neuropathy, whereas the patients without microvessel changes did not develop neuropathy (Malik et al., 2005).

2.9.2.2 Dry skin and fissures

Skin manifestations in T2DM are found to be very common with frequency 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 patients suffer from a skin condition (Demirseren et al., 2014). In a study conducted on 750 subjects with DM it was 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)

Dry skin is the first and most common among the cutaneous manifestation seen in subjects with T2DM because of 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 autonomic neuropathic system, the skin's endothelial cells get damaged and this may even reduce its ability to sweat which leads to dry skin, fissure and callus formation as well as decrease in the ability to sense temperature and pressure (Petrofsky et al., 2012).
2.9.2.3 Calluses

Calluses are flat areas of tough, thickened skin caused by repeated pressure or friction against the foot. It’s a body’s mechanism to protect the internal skin by thickening external skin surface into thick and hard to prevent less exposure of internal skin to high temperature, cold or penetration. Several studies documented that T2DM subjects with PN are always associated with callus formation. Loss of sensation, loss of proprioception and toe deformities caused due to peripheral neuropathy is considered to be the major factor responsible for the development of callus. (Fernando et al., 2014) The most frequent deformities like the hammer toes and claw toes are found to be a significant factor in the structural foot changes that often result in increase in pressure in certain areas of plantar aspect of the foot leading to callus formation which further increases the plantar pressures.(Smith et al., 2000) Areas of the foot where the plantar pressures are high are at high risk for foot ulceration.

In a study conducted by Murray et al. has reported a 57% risk for ulcer incidence at high pressure points and also in this study they also documented the relationship between callus and ulcer risk sites, which may be a consequence of excessive shear forces which was documented in previous studies that friction forces cause hyperkeratosis of the tissues. (Murray et al.,1996; M Yavuz et al., 2007; Metin Yavuz et al.,2008). In a study conducted by Antonella et al, it was also documented that forefoot is more at risk for callus formation as compared to rear foot which was dependent on the severity of peripheral neuropathy. In their study they found increased plantar pressure both on the forefoot and the rear foot, whereas, the ratio between forefoot and rear foot pressure is increased in case of severe peripheral neuropathy.(John et al., 2002) In another study conducted by Mueller et al.
concluded that peak plantar pressure is more in forefoot compared to rear foot which may lead to callus formation and injury to the underneath skin which is considered to be the risk factor for ulcer formation. (Mueller et al., 2005)

2.9.2.4 Ingrowing nails

Most of the findings that are observed in the toenails of the T2DM subjects may be characterized with descriptive terms such as, normal dysmorphic (irregularly shaped), hypoplastic, dystrophic (showing abnormal growth from the nail matrix), thickened (from fungal infection), discolored (from subungual hematoma), fissured and avulsed nail bed. (Khunger & Kandhari, 2012) In the general population ingrown nail is a relatively common disease, accounting for up to 50% of all nail disorders. (Effendy et al., 2005; Scher et al., 2007; Seebacher et al., 2007). Several studies have shown a prevalence of ingrown nails ranging from 2-13% in the general population. (Cribier et al., 2004a). Approximately 10% of the general population, 20% of the population aged>60 years up to 50% of people aged>70 years and up to one-third of T2DM individuals have ingrown nails (Thomas et al., 2010).

Romano et al. found that non-diabetic subjects had a higher prevalence of ingrown than T2DM subjects (1.8% vs. 1.2%). They observed no correlation between dermatophyte infections and the duration or type of diabetes, or blood sugar levels or levels of HbA1c. (Romano et al., 2001a). This is in contrast to studies by Dogra et al and Pierard – Franchimont, the prevalence of ingrown nails in T2DM subjects was significantly higher than in non-diabetic subjects (17% vs. 6.8%). (Dogra et al., 2002; Pierard et al., 2005) Thus, T2DM subjects were found to be 2.5-fold more likely to have in grown nails and it is associated with the duration of the diabetes.
2.9.2.5 Hammer/claw toes

Hammer toe is a deformity of the proximal interphalangeal joint of the toes. Studies documented that atrophy of the intrinsic muscles of the foot, as a consequence of motor neuropathy leads to fixed claw toe deformities which are common in the feet of diabetic subjects with peripheral neuropathy. (SA Bus et al., 2009) In a study conducted by William R. Ledoux, on high risk 398 diabetic population and observed 46.7% of the diabetic population had hammer/claw toe deformity. (Ledoux et al., 2005) whereas, in another study conducted in Iraq it was concluded that 5.4% hammer/claw toe deformity were observed in diabetic population.(Mansour et al., 2006). Very high prevalence of 45.43% of hammer/claw toe deformity were seen in a study by Miulescu et al on diabetic population with distal symmetric polyneuropathy.(Miulescu et al., 2014). 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. (Kumar et al., 2015, SA Bus et al., 2009, Sicco a. Bus et al., 2002, Severinsen, 2007)

2.9.2.6 Fungal infections

T2DM subjects represent a unique group of individuals who are more prone to develop infections than non-diabetic individuals. The growing diabetic population in India and lack of knowledge about foot care present a considerable health problem. (Manisha C et al 2013) Fungal foot infection is diabetic dermopathy which includes the most frequent mycological infections in the form of both tinea pedis (skin infection) and onychomycosis (nail infection). (Bristow & Spruce, 2009) Foot fungal infections occurs in one-thirds of patients (Piérard-Franchimont et al., 2009) and increases the risk of developing diabetic
foot syndrome - a major reason for disability and mortality in diabetic subjects, particularly men (Robbins et al., 2003; Grover et al., 2003; Cribier et al., 2004).

According to Mayser et al. 24, 82.1% of 95 patients with diabetes mellitus had clinical signs of dermatomycosis or onychomycosis and 84.6% of these patients tested positive microscopically or by culture. (Mayser et al., 2004) Studies performed by Eckhardt et al. 25 and Romano et al. 26 have found Trichophyton rubrum to be the most common pathogen. (Eckhard et al., 2007; Romano et al., 2001b) Contrary to these findings, a number of other studies have demonstrated Candida spp. to be the most commonly isolated fungal species in diabetic foot patients. Fata et al., for example, found a 20% prevalence of fungal infections in diabetic foot patients, caused mainly by various species of Candida spp., especially Candida albicans (Fata et al., 2011). Mlinarić-Missoni et al reported on Candida parapsilosis as the most frequent causative agent in diabetic foot ulcers, followed by seven other Candida species (Mlinarić-Missoni et al., 2005).

In a study conducted by Wijesuriya et al documented that out of 385 diabetic subjects 66% were mycologically confirmed to have superficial fungal foot infections. Non dermatophyte fungal species were the most common pathogen causing fungal infections, followed by yeast and dermatophyte fungal species. Nail infections were the commonest type of superficial fungal foot infections among the study population which is in agreement with the study done by Yehia et al. (Yehia et al., 2010) Among the patients who were clinically suspected to have superficial fungal foot infections 14% showed negative culture results, even though they had been clinically suspected to have superficial fungal foot infections. (Weerasekera et al., 2014) Therefore fungal infections are commonest form of
infections seen in subjects with T2DM which are a risk factor for the formation of ulcers and further complications.

### 2.9.2.7 Diabetic foot ulcers

Foot ulceration is the most common complication affecting approximately 15% of diabetic patients during their lifetime (Shankhdhar et al., 2008, Singh et al., 2005). This can be attributed to several social and cultural practices such as barefoot walking, inadequate facilities for diabetes care and education, and poor socioeconomic conditions. (Dixit & Kumar, 2014; Dixit et al., 2011) Sporadic qualitative research suggests that diabetic foot ulceration has a profound social impact with patients reporting social isolation, loss of social role, and unemployment. (Habib et al., 2010) In UK and USA the prevalence of foot ulceration due to diabetes has found to be 5-7% (Kerr, 2012) respectively, whereas in the developing countries it has shown a higher percentage (A. Boulton et al., 2005; Riaz et al., 2014).

In a developing country like India, the prevalence of diabetic foot ulcers were found to be very high. In a study conducted by Shahi et al., on T2DM population in North India found that 14% of the diabetic population had foot ulcers among 87% of diabetic 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 urban population. (Shahi et al., 2012) In another study on South Indian population documented that 41.51% of the diabetic population were with non healing 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. Peripheral vascular disease (PVD) was frequent in Germany, while in Tanzania and Chennai, India, it was far less common. A lesser prevalence of PVD, and yet higher prevalence of amputation rate among Indians was noted when compared with those in Western countries because of progressive infection (Tanzania vs Germany vs India: 12% vs 48% vs 13%, respectively) (Viswanathan et al., 2007).

Diabetic foot ulceration can develop because of acute or chronic cutaneous compromise of the skin, arterial insufficiency, DPN or a combination of these factors. 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., neuroischemia). The prevalence of PAD among those with foot ulcers has recently been shown to be increasing and now the majority likely has PAD or neuroischemia (Margolis et al., 2011).
SECTION 6

2.10 Assessment of diabetic foot

Foot complications are the common complication observed in long-term T2DM. PN is considered to be the major risk factor for developing major foot complications like foot ulcers and amputation. Early recognition and management of risk factors is important for reducing morbidity of foot ulceration. Most risk factors are readily identifiable from the history or clinical examination. (Damir et al., 2011)

Components of foot assessment in T2DM

a) Neurological assessment
b) Vascular assessment
c) Musculoskeletal assessment
d) Biomechanical assessment

2.10.1 Neurological assessment

The two most prominent changes on neurological examination will be, reduced or lost ankle reflexes and a distal gradient loss of large and small sensory fiber modalities or “stocking and gloves” sensory loss. (Dixit S et al., 2015) This can be examined through a simple clinical examining of protective sensation of the feet by using Semmes-Weinstein 10gm monofilament and Vibration perception Threshold (VPT) using Biothesiometer.

2.10.1.1 Monofilament Testing

Performing monofilament testing on the plantar surface of great toe and pulp of the index finger bilaterally can assess sense of touch. The current available device is known as Semmes-Weinstein monofilaments (SWM). They are usually made of fine nylon and are
designed in a way that the amount of pressure on the plantar surface is the function of instrument not the examiner. The higher the value of the monofilament, the stiffer and more difficult it is to bend and applies more pressure. In common clinical practice usually three monofilaments are used to diagnose peripheral neuropathy. They are 4.17, 5.07 and 6.10. (Dros et al., 2009) Each monofilament is marked with a number that represents the decimal log 10 times the force in milligrams from 1.65 (0.45gm) to 6.65 (447gm) of linear force. The sensitivity of monofilament ranges from 0.41 to 0.93 and specificity varies from 0.68 to 1. The examiner should also be sure to avoid callus area. Subjects without PN should be able to sense 3.61 monofilaments (equivalent to 0.4gm of linear force). The ability to sense 4.17 (equivalent to 1gm of linear force) or higher is considered consistent with PN, inability to sense 5.07 is consistent with loss of protective sensation (Dros et al., 2009).

2.10.1.2 Vibration perception threshold

Use of the vibration perception threshold (VPT) is a simple way of detecting large-fiber dysfunction thus identifying individuals with diabetes at a risk of ulceration. (A. J. Boulton et al., 2005) Traditionally, vibration perception has been measured with a 128Hz tuning fork. There are several methods for testing vibration which are available to quantify vibration perception like Vibrotip, Neurotip, Vibraton, Neurothesiometer and Biothesiometer. Out of all the other devices Biothesiometer is considered to be accurate with specificity of 80 to 95% in quantifying the vibration threshold and used as a standard for the diagnosis of peripheral neuropathy. (Perkins et al., 2001; M. Malik et al., 2013) Biothesiometer consists of a vibration probe that vibrates at 100Hz with an amplitude varying from 0 to 50 volts. Studies show that VPT more than 25volts in vibration threshold is a strong predictor of future ulceration.
2.10.1.3 Deep tendon reflexes

Documentation of ankle and knee reflexes is an important part of physical examination which has a sensitivity of (81.09%), specificity (81.679%) with diagnostic accuracy of (81.22%) in T2DM subjects with known or suspected PN. (M. Malik et al., 2013) Ankle reflex or muscle stretch reflexes are diminished or absent in T2DM with peripheral neuropathy. In neuropathy as the duration of diabetes increases to 15-20 years it is common for the arms and legs to become areflexic; Upper limb reflexes are usually preserved in early diabetic yet as the disease progresses they either become reduced or absent.

2.10.2 Vascular assessment

Peripheral arterial disease (PAD) is a component cause in approximately one-third of foot ulcers and is often a significant risk factor associated with recurrent wounds. (Edgar J.G. et al 2007) Therefore, the assessment of PAD is important in defining overall lower-extremity risk status. Vascular examination should include palpation of the posterior tibial and dorsalis pedis pulses which should be characterized as either “present” or “absent”. (Khan et al., 2006) Consequently, in addition to clinical parameters, non-invasive measures of circulation are frequently used to complement physical examination in assessing the degree of arterial obstruction. More reliable methods of assessing peripheral vascular status involve measurement of Ankle Brachial Index, systolic toe pressure measurements or measurement of distal transcutaneous oxygen tension (TcPo2). (Damir et al., 2011)
2.10.2.1 Ankle brachial Index (ABI)

The ABI is a simple and easily reproducible method of diagnosing vascular insufficiency in the lower limbs. Blood pressure at the ankle (dorsalis pedis or posterior tibial arteries) is measured using a standard Doppler ultrasonic probe. The ABI is obtained by dividing the ankle systolic pressure by the higher of the two brachial systolic pressures. (ADA, 2003) An ABI >0.9 to <1.3 is normal (Khan, 2006). ABI <0.8 is associated with claudication, and <0.4 is commonly associated with ischemic rest pain and tissue necrosis. ABI may therefore be part of the annual comprehensive foot exam in these patient subgroups. Although the ABI is used to indicate adequacy of peripheral blood flow in patients without diabetes, the ABI is less reliable in diabetic patients because calcification of the media of the distal arteries is common. This calcification makes the vessels relatively non-compressible, resulting in high systolic pressure in the ankle or supra-systolic ankle pressures. In the presence of incompressible calf or ankle arteries (ABI >1.3), measurements of digital arterial systolic pressure (toe pressure) by photo plethysmography or transcutaneous oxygen tension (TcPo2) may be performed. Both these latter assessments are performed in specialty diabetic foot clinics or vascular laboratories and offer an indication of potential for healing before angiography is considered. A contrast angiogram remains the criterion standard of assessment in patients with peripheral vascular problems but has to be undertaken with caution among patients with diabetes who often already have nephropathy.

2.10.3 Musculoskeletal assessment

The musculoskeletal assessment should include evaluation for any gross deformity. Rigid deformities are defined as any contractures that cannot easily be manually reduced
and are most frequently found in the digits. Common forefoot deformities that are known to increase plantar pressures and are associated with skin breakdown include metatarsal phalangeal joint hyperextension with interphalangeal flexion (claw toe) or distal phalangeal extension (hammer toe). An important and often overlooked or misdiagnosed condition is Charcot arthropathy. This occurs in the neuropathic foot and most often affects the midfoot. This may present as a unilateral red, hot, swollen, flat foot with profound deformity. Studies reported that most of these complications occur as a result of uncontrolled blood sugar levels, which leads to altered blood supply to the feet which further leads to atrophy of intrinsic foot muscles. Addressing these changes are well developed through imaging of the diabetic foot.

### 2.10.3.1 Medical Imaging in diabetic foot

Medical imaging of the diabetic foot entails a variety of imaging modalities. The diagnostic evaluation often includes a gamut of studies that include conventional radiography, CT, MRI, ultrasonography, and a newcomer, positron emission tomography combined with CT (Ranachowska et al. 2010) Diagnostic imaging aims to determine musculoskeletal changes caused as a result of DM, infectious neuroarthopathies and vasculopathies.

A meta-analysis by Dinh et al. documented the sensitivity and specificity of diagnostic imaging devices through stratifying the utility of diagnostic tests in the diabetic foot. (Dinh et al., 2008) Bone biopsy has a sensitivity of 60%, specificity 91%, plain X-ray 54% and 68%, MRI 90% and 79%, and radiolabelled granulocytes scintigraphy 74% and 68%, respectively. The authors believe that the best tests for diagnosing osteomyelitis are bone probing, bone biopsy, and, among imaging modalities, MRI scanning. Butalia et al.
believe that the clinical data are decisive. An area of ulceration larger than 2 cm², blood sedimentation rate above 70 mm/h, positive bone biopsy, and positive plain X-ray results are sufficient to diagnose bone involvement. In dubious cases MRI scanning may aid the diagnosis. (Butalia et al., 2008) Other authors believe that the imaging should be started with plain X-ray, particularly if Charcot’s osteoarthropathy and bone infection is granulocyte scanning, preferably performed at the same time as MRI.

Considering the exposure to MRI radiation and the cost of the procedure recent literature also documented Musculoskeletal ultrasonography as a reliable procedure as a diagnostic imaging device. (Kumar et al., 2015; Patil et al., 2012; Sanverdi et al., 2012) In a study conducted by Kaare et al to evaluate a bedside test with ultrasonography for the evaluation of intrinsic foot muscles, and found atrophy of intrinsic foot muscles determined at ultrasonography is directly related to foot muscle volume determined by MRI. (Severinsen et al., 2007) In conclusion, there are various data on diagnostic imaging of diabetic foot for the detection of foot complications. Even though there is “no best test”, some authors believe that imaging should be started with plain x-ray for the imaging of the bony structure of the diabetic foot and musculoskeletal ultrasound as a reliable imaging device for assessing soft structures of the diabetic foot.

2.10.3.2 Biomechanical assessment (Kinetics and kinematics) of foot in T2DM

2.10.3.2.1 Kinetic foot evaluation

Kinetic evaluation of the diabetic foot is mainly focused to analyze the plantar pressures under 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, change in muscle strength, motor/sensory neuropathy, and change in structure/deformity of the feet.

Studies documented that plantar pressure in diabetic 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; Mueller et al 2002; Viswanathan et al 2003).

Plantar pressure evaluation systems available on the market or in research laboratories vary in sensor configuration. Typically the configuration is one of three types: pressure distribution platforms, imaging technologies with sophisticated image processing software and shoe systems. The key requirements for these devices are spatial resolution, sampling frequency, accuracy sensitivity and calibration. (Gefen et al., 2007) Among all the devices, pressure distribution platforms like F-scan (R2=0.97) (Luo et al., 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 (Syed et al., 2013).

The forefoot is considered the commonest area of the foot where peak plantar pressure is seen and risk for ulceration. Ulcers commonly occur under the first, second, or third metatarsal head, and most neuropathic ulcers result from excessive and repetitive
pressure applied to the foot while walking. (S. C. Wu et al., 2007) Several contributing factors lead to diabetic foot ulceration, such as peripheral neuropathy, foot trauma, foot deformity, increased foot pressures, and callus. Thus, foot ulcers develop as a consequence of a combination of intrinsic factors, such as reduced sensation, and extrinsic mechanical factors, such as high plantar pressures caused by abnormal mechanical loading of the foot. Therefore plantar pressure analysis in the early course of the diabetes mellitus plays a major role in identifying the risk of developing an ulcer.

2.10.3.2.2 Kinematic foot evaluation

Kinematic foot evaluation includes analysis of gait characteristics like spatiotemporal parameters which include gait velocity, stride length, step duration, gait cycle duration and gait cycle length gets altered due to structural and mechanical changed caused by T2DM. (Hastings et al., 2014a, 2014b; Mcdonald et al., 2012; Sawacha et al., 2009; Sinclair et al., 2014; Zequera et al., 2013). Several advanced analysis systems like Win-track (ICC 0.75 to 0.90), Vicon 3D motion analysis (ICC=0.774), Xsens 3D motion tracking (ICC 0.84 to 0.90), Visual 3d Qualisys motion capture, Simi motion2D/3D (0.51 to 0.76), Noraxon etc. are used to obtain these spatiotemporal gait parameters and joint angles.

In a met-analysis by Malindu Fernando in 2013 reported that gait velocity was significantly reduced in subjects with T2DM compared to subjects with no DM. (M. Fernando et al., 2013) Similar to this study, a study conducted by Nagwa M.H et al in 2010 observed a significant reduction in walking velocity, cadence, stride length, stance time, gait cycle duration angles of ankle and knee joints as compared with non-diabetic subjects. In contrast to our results, Dingwell et al. evaluated kinematics of diabetic gait. They found a non-significant decrease in gait cycle time (sec) in evaluated diabetic group (1.22sec for
the control group versus 1.21 sec for the diabetic group). (Dingwell et al., 2001). In a study by Menz, et al. who compared the spatiotemporal parameters of the gait of 30 elderly diabetics with peripheral neuropathy to 30 age-matched controls and found a significant alterations in spatiotemporal parameters in T2DM subjects as compared to non-diabetic subjects. (Menz et al., 2004). In another study on both diabetic subjects with and without peripheral neuropathy compared with non-diabetic subjects, it was revealed that diabetic subjects with and without peripheral neuropathy had slower gait, shorter steps and limited knee and ankle mobility than the non-diabetic group. Therefore it was concluded that neuropathy may not be the only reason for gait deviations in DM patients. (Yavuzer et al., 2006)

Allet, et al. in their systemic review about gait deviations in diabetic patients and conducted a clinical observation study as gait was assessed on three different real life surfaces (tar, grass, and stones). Diabetic patients' gait parameters differed significantly from those of healthy controls. They concluded that walking in real life conditions revealed gait difficulties in patients with diabetes before neuropathy was clinically detectable and clinicians should be aware that diabetic individuals' gait capacity decreases and fall risk increases at an early stage of the disease. (Allet et al., 2009) If gait analysis is included in the assessment of patients with diabetes mellitus and gait alteration is detected it should be taken as a warning sign. This is reported to be related to a increased risk of fall. The application of prevention strategies is thus shown to be imperative.

Therefore, it is concluded that T2DM subjects show significantly lower walking velocity, cadence, stride length, step duration, gait cycle length and angles of the ankle and knee joints (degrees) as compared to non-diabetic subjects, whereas, stance time percentage and time of gait cycle (sec) in T2DM group remains significantly higher.
SECTION 7

2.11 Quality of life in diabetic foot (QOL)

WHO in 1948 defines QOL as "A state of complete physical, mental, and social well-being not merely the absence of disease". The diabetic population are prone to early complications leading to a poor quality of life and increased mortality. Foot ulcers as a result of peripheral neuropathy and vasculopathy are the leading cause of amputations. (Lee et al., 2013) Usually, there is a poor QOL reported in patients with diabetic foot ulcers in comparison with the general population and patients with T2DM.

Ashford et al assessed QOL of 21 patients with diabetic foot ulcers and reported some procedures that their families were unable to follow, causing familial problems which had negative effects on their quality of life such as wound dressing and limited daily activities. (Ashford et al., 2000) A study done by Nabuurs-Franssen et al in 2005 revealed that patients with healed ulcers had a better QOL than patients with persisting ulcers. It also appears to be an emotional burden on the patient’s caregiver, hence revealing the seriousness of the situation in foot complications like ulcers. (Nabuurs-Franssen et al., 2005) Furthermore, the location of foot ulcer is one of the factors affecting the QOL which affects dimensions such as enjoying life, physical health, negative emotions and wound care difficulties, worsening the quality of life. Ribu et al in 2007 concluded that the QOL life in patients with diabetic foot ulcers has a significant relationship with the wound location, especially when it is in plantar and heel regions. (Ribu et al., 2007) Whereas, a study by Valensi stated that patients whose ulcers were located in heel or dorsalis pedis region had better QOLs than the ones who developed wounds in their plantar regions or under their toes. (Valensi et al., 2005)
SECTION 8

2.12 Lifestyle interventions in t2dm

2.12.1 Physical activity

2.12.1.1 Aerobic exercise in T2DM

Prevalence of T2DM progressively affects younger and middle-aged population worldwide. In 2013 there were 382 million people with diabetes, and this is expected to rise to 592 million (55%) by 2035. (Aguiree et al., 2013) Population growth, aging, urbanization, changing lifestyle, Physical activity, and dietary habits signifies in global epidemiology for T2DM and its complications which are on the verge to rise in the Indian population (Cheema et al., 2014; Ramachandran et al., 2012).

Lifestyle intervention programs consisting of glucose control through medication, exercise prescription with or without dietary modulation has been 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), and 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 (Tan et al., 2014).

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, 75 minutes of vigorous-intensity aerobic activity, or a combination of both for adults. It is advised to follow the FITT (F=frequency, I=Intensity, T=Time, T=Type) principle to design and implement a safe effective exercise program.

Exercise guidelines for type 2 diabetes mellitus (ACSM)

<table>
<thead>
<tr>
<th>Mode</th>
<th>Frequency, Intensity, Duration</th>
</tr>
</thead>
<tbody>
<tr>
<td>Aerobic exercises</td>
<td>At least 3 to 5 days/week</td>
</tr>
<tr>
<td></td>
<td>Mild to moderate Intensity (40-60% VO₂ max, RPE of 11-13 on a 6-20 Borg’s scale)</td>
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<tr>
<td></td>
<td>Minimum 150 minutes/week</td>
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<tr>
<td></td>
<td>Exercises involving larger group muscles</td>
</tr>
<tr>
<td></td>
<td>Slow progression of intensity, duration, and frequency</td>
</tr>
<tr>
<td>Resistance exercises</td>
<td>Two sessions per week</td>
</tr>
<tr>
<td></td>
<td>5 to 10 types of exercises involving major muscle groups</td>
</tr>
<tr>
<td></td>
<td>3 to 4 sets per exercise</td>
</tr>
<tr>
<td></td>
<td>Each muscle 10 to 15 repetitions per set</td>
</tr>
<tr>
<td>Flexibility exercises</td>
<td>Stretching exercises for 5 to 10 minutes before and after aerobic or resistance training</td>
</tr>
</tbody>
</table>

**Frequency:** Research shows that moderate to vigorous exercise makes muscle and fat cells sensitive to insulin for up to 48 hours. (Turcotte et al., 2008) Considering this beneficial mechanism, ACSM guidelines recommend performing exercise 5 days of exercise/week of moderate intensity for 40 minutes each session. (Colberg et al., 2010)

**Intensity:** Based on the ACSM and ADA guidelines aerobic exercises are recommended at least at moderate intensity, corresponding approximately to 40–60% of VO₂max or
40%-60 % of heart rate reserve has been proved to be beneficial in controlling blood glucose and increasing insulin sensitivity in T2DM (maximal aerobic capacity). For most people with T2DM, brisk walking is a choice of activity which is a moderate-intensity exercise. Additional benefits may be gained from vigorous exercise (60% of VO2max). Studies have proven that exercise intensity predicts improvements in overall BG control to a greater extent than exercise volume, suggesting that those already exercising at a moderate intensity should consider undertaking some vigorous physical activity to obtain glycemic control. (Balducci et al., 2009; Colberg et al., 2010; Larose et al., 2010)

**Time/Duration:** Individuals with T2DM should engage in a minimum of 150 minutes/week of exercise undertaken at moderate intensity or greater. Aerobic activity should be performed in bouts of at least 10 minutes and be spread throughout the week. Around 150 minutes/week of moderate-intensity exercise is associated with reduced morbidity and mortality in observational studies in all populations.

**Mode:** Both aerobic and resistance training has proven to be beneficial and has important roles in type 2 diabetes. The combination of both forms of training was twice as effective for improving glycemic control. Any form of exercises that uses large muscle groups and causes sustained increases in heart rate is likely to be beneficial, and undertaking a variety of modes of activities are recommended (Colberg et al., 2010).

**The rate of progression:** At present, no study on individuals with T2DM has compared rates of progression in exercise intensity or volume. Gradual progression of both is advisable to minimize the risk of injury, particularly if health complications are present and to enhance compliance (Colberg et al., 2010).
2.12.1.2 Resisted exercises

Resistance training is a therapeutic tool which has the potential to improve muscular strength, endurance, enhance flexibility, enhance body composition, and decrease risk factors for cardiovascular disease which are commonly encountered. ADA recommended a minimum of 8 to 10 exercises involving a major group of muscles with one set of 10-15 repetitions with warm up and cool down exercises for 5 – 10 minutes regularly. Resistance training has been shown to improve insulin-stimulated glucose uptake in patients with T2DM and likewise to improve muscle strength in elderly subjects with or without T2DM. (Dela et al., 2006) Studies documented that resistance exercise in combined with aerobic exercises plays a more beneficial role in controlling blood glucose levels. A randomized controlled study by Sigal et al. showed that both aerobic training and resistance training alone improve glycemic control in patients with T2DM (Sigal et al., 2007).

A recent study conducted by van Dijk et al. concluded that a single session of resistance- or endurance-type exercise reduces the prevalence of hyperglycemia and improves glycemic control during the subsequent 24 hour period in individuals with impaired glucose tolerance and in insulin-treated and non-insulin-treated T2DM patients. Despite these short-term and relatively long-term randomized controlled trials it is still not well known whether increased volume or combination of training modalities is more important than exercise type. (Van Dijk et al., 2012) Furthermore, the mechanistic differences between the two training modalities in improving glycemic control are unclear.
2.12.1.3 Foot strengthening in T2DM

T2DM is associated with an increased risk of falls caused by many factors, such as loss of protective sensation, atrophy of the intrinsic foot muscles and limited joint movements. Wallace et al. reported an overall incidence of falls of 1.25 falls per person in a year in T2DM subjects.

Loss of protective sensation and atrophy of intrinsic foot muscles leads to changes in gait, a major risk factor forfalls in T2DM (Petrofsky et al., 2012, Yavuzer et al., 2006). Even though it is well documented on atrophy of intrinsic foot muscles are seen in long-term T2DM subjects (Andersen et al. 2004; SA Bus et al., 2009; Sicco a. Bus et al., 2002; Kumar et al., 2015) and this puts the foot in danger by causing deformed toes and increased plantar pressures and ulcers. There still remains a dearth of literature in strategies to prevent atrophy of intrinsic foot muscles.

2.12.1.4 Self-management in T2DM and foot complications

Self-management education (SME) is defined as a systematic intervention that involves active patient participation in self-monitoring (physiological processes) and/or decision making. (Chodosh et al., 2005) It recognizes that patient-provider collaboration and the enablement of problem-solving skills are crucial to the individual's ability for sustained self-care (Bodenheimer et al., 2002).

The goals of management for patients with T2DM include optimization of blood glucose control, prevention of early and late complications. All the treatment factors, diet, medication, and exercise must be carefully managed on a daily basis by patients themselves. Patients must be able to recognize when they need professional help. Good
self-management 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. (Haas et al., 2012) Because patients are responsible for the day-to-day control of diabetes and its complications.

Several programs are established aiming to educate the diabetes patients to control diabetes and prevent complications. The National Institute for Health and Care Excellence (NICE) patient education program, Patient Education Working Group (PEWG), Diabetes Education and Self-Management for Ongoing and Newly Diagnosed (DESMOND), Diabetes X-PERT program are some of the programs developed to educate the patients for optimizing diabetes control and prevention of complications.

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-management into their daily lives. Several meta-analyses have demonstrated that SME is associated with clinically important benefits in persons with T2DM, such as reductions in glycated hemoglobin (hbA1C) of 0.36% to 0.81%. (Chodosh et al., 2005; Gary et al 2003; Minet et al 2010) Improved QOL for persons with either T1DM or T2DM also has been demonstrated (Cochran & Conn, 2010), as have other important self-care outcomes in those with T2DM, such as sustained weight loss and cardiovascular fitness for up to 4 years. (Wing, 2010) One systematic review involving both T1DM and T2DM found that, as measures progressed from immediate to long-term outcomes, percentage of improved outcomes reduced (immediate learning 78.6%, intermediate behavior change 50.0%, long-term clinical improvement 38.5%. (Boren et al., 2007) A 5-year follow-up of a patient-
centered T2DM SME program resulted in no worsening of hbA1C, whereas the hbA1C in the control group rose 1.3% over the 5 years (Hörnsten et al., 2008).

In conclusion, there has been a clear increase in the use of multifaceted programs that incorporate behavioral/psychosocial interventions, as well as knowledge and skills training, with a marked reduction in didactic educational programs that focus on knowledge or skill acquisition only. Interventions that include face-to-face delivery, a cognitive-behavioral method and the practical application of content are more likely to improve glycemic control. The most effective behavioral interventions involve a patient-centered approach, shared decision making, the enablement of problem-solving skills and the use of action plans directed toward patient-chosen goals. However in India there is a dearth of literature on self-management in T2DM. Future studies need to incorporate self-management program in optimizing blood glucose and preventing and managing complications of T2DM.

2.12.1.5 Diet in T2DM

A healthful eating pattern, regular physical activity and often pharmacotherapy are the key components of diabetes management. For many patients with DM the most challenging part of the treatment plan is determining on a diet. Several studies demonstrated that effectiveness of diet on improving glycemic control, various markers of cardiovascular and hypertension risk. (Andrews et al., 2011; Evert et al., 2013; Steyn et al., 2004; Thompson et al., 2014)
Carbohydrates: The carbohydrates are usually defined as sugars, starch, and fibers. A number of factors influence glycemic responses to foods, including the amount of carbohydrate, type of sugar, nature of the starch, cooking and food processing, and food form, as well as other food components. Some published studies comparing lower levels of carbohydrate intake (ranging from 21g daily up to 40% of daily energy intake) to higher carbohydrate intake levels indicated improved markers of glycemic control and insulin sensitivity with lower carbohydrate intakes (Kahleova et al., 2011; Kodama et al., 2009; Miyashita et al., 2004).

Dietary fiber: Intake of dietary fiber is associated with lower all-cause mortality in people with diabetes. (H. Wu et al., 2015) Two systematic reviews found little evidence that fiber significantly improves glycemic control. (Franz et al., 2010; Wheeler et al., 2012) Studies published since these reviews have shown modest lowering of preprandial glucose (Post, Mainous, King, & Simpson, 2012) and A1C (2 0.2 to 2 0.3%) (Jenkins et al., 2002) with intakes of .50 g of fiber/day.
2.13 Medical management of T2DM

The diagnosis of T2DM is often delayed, and 20% to 50% of people with T2DM present with microvascular and/or macrovascular complications at the time of diagnosis. When lifestyle interventions fail to control blood glucose levels adequately pharmacological treatment becomes necessary. Due to the progressive nature of T2DM the majority of diabetic subjects eventually require hypoglycemic drugs and many will require combination hypoglycemic drugs including insulin. (NICE Clinical Guidelines 87, 2009) The choice of the hypoglycemic drug needs to be individualized to the patient. While the efficacy of the various therapies at lowering glucose is similar, hypoglycemic drugs have different side effect profiles and may have the potential advantage of modifying cardiovascular risk factors such as lipid profiles

2.13.1 Oral Hypoglycemic agents

Most patients should begin with lifestyle changes (lifestyle counseling, weight-loss education, exercise, etc.). When lifestyle efforts alone have not achieved or maintained glycemic goals, metformin should be added at, or soon after, diagnosis, unless there is contraindications or intolerance. Metformin is the drug of the first choice for people with T2DM who have inadequate glycemic control after 3 months of making lifestyle changes. (Harper et al., 2013) Metformin has a long-standing evidence base for efficacy and safety, is inexpensive and may reduce the risk of CV events (Holman et al., 2008).
Sulfonylurea may be used if metformin cannot be tolerated. The combination of drugs is used if target blood glucose levels are not achieved after titrating metformin (or a sulfonylurea) to the highest tolerated dose for 3-6 months (Harper et al., 2013).

A comparative effectiveness meta-analysis suggests that overall each new class of oral hypoglycemic agents added to initial therapy lowers A1C around 0.9-1.1%. If the A1C target is not achieved after approximately 3 months consider a combination of metformin and one of these six treatment options: sulfonylurea, thiazolidinedione, DPP-4 inhibitors, SGLT2 inhibitors, GLP-1 receptor agonists, or basal insulin. Drug choice is based on the patient’s preferences as well as the various patient, disease, and drug characteristics, with the goal of reducing blood glucose levels while minimizing side effects, especially hypoglycemia (Bennett et al., 2011).

Historically the preferred medicine to add as second-line therapy has been sulfonylurea, as it is the most cost effective and is supported by decades of clinical experience. However, alternative approaches include introducing one other oral glucose-lowering medicine (thiazolidinedione, DPP4 inhibitor, acarbose, SGLT2 inhibitor) or if the patient is willing to self-inject, insulin or a GLP1 agonist is considered in addition to lifestyle measures, adherence to medicines and dose titration. (García-Pérez et al., 2013) Insulin is the preferred drug for people with inadequate glycemic control despite taking maximally tolerated doses of oral glucose-lowering agents.
2.13.2 Insulin therapy

Equipping patients with an algorithm for self-titration of insulin doses based on self-monitoring of blood glucose improves glycemic control in T2DM patients initiating insulin. (Blonde et al., 2009) Basal insulin alone is the most convenient initial insulin regimen, beginning at 10 U or 0.1-0.2 U/kg, depending on the degree of hyperglycemia. Basal insulin is usually prescribed in conjunction with metformin and possibly one additional noninsulin agent. Options include adding a Glucagon-like Peptide1 receptor agonist or mealtime insulin, consisting of one to three injections of rapid-acting insulin analog (lispro, aspart, or glulisine) administered just before eating.
SECTION 10

2.14 Summary of the literature review

The prevalence of diabetes is rapidly increasing and is expected to reach epidemic proportions over the next decade. Today, nearly 415 million people worldwide are diagnosed with diabetes, with India accounting for 69.2 million. (IDF 2015) Diabetes is associated with many complications of which foot complications are considered to have very high prevalence. (Aguiree et al., 2013) The majority of the diabetes population are aged between 40 and 59, and 80% of them live in low- and middle-income countries.

T2DM is associated with macrovascular and microvascular complications of which musculoskeletal and foot complications are considered to have very high prevalence, there is a dearth of literature on prevalence of musculoskeletal and foot complications in subjects with T2DM in Indian population (RP Narwhal et al., 2004, Dixit S & Maiya A 2014).

Several studies have documented that aerobic exercises are very effective in enhancing the glycemic control. Whereas, in developing country like India, foot is the most ignored part of diabetes evaluation and management. Therefore the present study focuses on estimating the prevalence of musculoskeletal and foot complications in subjects with T2DM and to identify the effect of structured foot health program on foot biomechanics in subjects with T2DM.