Chapter 1
INTRODUCTION
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1.1 Background

Diabetes mellitus (DM) is a metabolic disorder characterized by hyperglycemia, which results from defects in insulin secretion, insulin action, or both. Deficiency in insulin leads to chronic hyperglycemia with disturbances of protein, carbohydrate, and fat metabolism. (ADA, 2014). Diabetes was first noticed by the ancient Indian Ayurvedic physicians, who observed flies and ants getting attracted towards the urine of people affected with certain diseases. After clinical tests by Indian physicians, it was named as ‘Madhumeha’ by Shushrutha. (Ahmed et al., 2002) Later after clinical experiments, DM is classified into type 1 diabetes mellitus (T1DM), type 2 diabetes mellitus (T2DM) gestational diabetes and other forms of diabetes. (ADA, 2014). Where, T2DM is the most common form of diabetes affecting 85-90% of the diabetic population. (IDF 2015)

1.2 Etiological classification of DM

1.2.1 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
1.2.2 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)

1.2.3 Gestational diabetes mellitus

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

1.2.4 Other specific types

- Genetic defect of insulin action (e.g. leprechaunism, lipodystrophies)
- Pancreatic disease (e.g. pancreatitis, pancreatectomy, neoplastic disease, cystic fibrosis, hemochromatosis, fibro calculous pancreatitis)
- Genetic defect of β-Cell function
- Excess production of hormonal antagonists to 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)

1.3 Global and national prevalence of DM

The prevalence of DM worldwide was estimated 415 million in 2015 and is expected to rise to 642 million by 2040. Most DM population live in low- and middle-
income countries and these will experience the greatest increase in cases of DM over the next 22 years. (IDF 2015) The possible reason for ‘Diabetes epidemic’ could be due to urbanization, population growth, longer survival, low physical activity, obesity and other factors. (Hu, 2011) The majority of the diabetic population are middle and younger age groups and 80% of them live in the middle and low-income countries. International Diabetes Federation (IDF 2015) reported that prevalence of diabetes mellitus may rise up to 55% by 2040. The present trend indicates Asia will hold the 60% of the world’s diabetic population, and where China to be the first country among the top 10 countries with India holding the second position (IDF 2015).

In the year 2000, it was estimated that the total number of people with diabetes in India were 31.7 million and it has also been named as “diabetes capital”. (Kaveeshwar & Cornwall, 2015) International Diabetes Federation (IDF 2015) estimated the total number of people in India with DM in 2015 were around 69.2 million and this is expected to rise to 123.5 million by 2040. (IDF 2015) Anjana et al in 2011 reported that the prevalence of DM in the rural population was one-fourth that of the urban population of India. The National Urban Survey conducted across the metropolitan cities of India reported a similar trend of the prevalence of DM 6.1 per cent in Kashmir (Northern India), 11.6 per cent in New Delhi (Northern India), 11.7 per cent in Kolkata (Eastern India), and 9.3 percent in West India (Mumbai) compared with 13.5 per cent in Chennai (South India), 16.6 percent in Hyderabad (South India), and 12.4 percent in Bangalore (South India) (Ahmad et al., 2011) (Ramachandran, Chamukuttan, Mohan, Diabetes, & Kem, 2015).
The rapid increase in the prevalence has made diabetes as one of the most important health hazards to all the nations. WHO estimates that in 2030 DM will be the 7th leading cause of death. In 2012, DM was the direct cause of 1.5 million deaths and more than 80% of deaths occur in low- and middle-income countries. (WHO, 2013) The primary determinants of the epidemic are the rapid epidemiological transition which is associated with urbanization, change in dietary patterns and decreased physical activity (Mohan, Sandeep, Deepa, Shah, & Varghese, 2007).

1.4 Complications of T2DM

T2DM is a metabolic disorder which is associated with microvascular and macrovascular complications. Hyperglycemia leads to functional and structural changes in the organs of the body like eyes, kidney, heart and nervous system. In a developing country like India, it was observed that among all the complications microvascular complications like foot and musculoskeletal complications are not given much importance at the early screening. (Dixit S, Maiya A, 2014)

1.4.1 Musculoskeletal complications in T2DM

T2DM may affect the musculoskeletal system in many ways. Studies documented that the development of musculoskeletal complications is dependent on the duration of diabetes mellitus and glycemic control. Musculoskeletal complications are generally not recognized in the early course of the DM as other complications like neuropathy, nephropathy, retinopathy and Vasculopathy. Musculoskeletal complications lead to illness, pain and physical disability placing high economic and personal burden. This burden includes the use of hospital and primary care services, disruptions to daily life, lost

The musculoskeletal manifestations of DM are the following syndromes of limited joint mobility, adhesive capsulitis (frozen shoulder, periarteritis), diabetic hand syndrome (diabetic Cheiroarthropathy), trigger finger (flexor tenosynovitis), Dupuytren’s contractures, osteoporosis, diffuse idiopathic skeletal hyperostosis (DISH), neuropathies, neuropathic arthritis, (Charcot joints, diabetic osteoarthropathy), Carpal tunnel syndrome, diabetic amyotrophy, reflex sympathetic dystrophy, various other neuropathies, diabetic muscle infarction. (Serban & Udrea, 2012)

In a study by Attar et al in 2012 documented a musculoskeletal complications on 18 of the 252 T2DM subjects the most common manifestations were carpel tunnel syndrome (91.1%), shoulder adhesive capsulitis (6.7%) and diabetic amyotroph (4.8%). They also documented the significant association between manual labor, overweight and vascular complications. (Attar, 2012) Whereas another study done by Douloumpakas et al in 2007, found 82.6% of the diabetic population manifested with musculoskeletal complications were mainly of non-inflammatory degenerative types (Douloumpakas et al 2007).

T2DM can affect the shoulder joint in several ways and shoulder adhesive capsulitis is considered to be the commonest among T2DM complications. Shoulder adhesive capsulitis or frozen shoulder is a rheumatological condition and it has been reported in 10-29% of the diabetic population. It is characterized by progressive, painful 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 and it is associated with duration of diabetes and age. (Lebiedz-Odrobina & Kay, 2010) studies documented that bilateral involvement is more frequent in patients with T2DM than in subjects without T2DM (Crispin & Alcocer-Varela, 2003).

Diabetic stiff hand syndrome or Cheiroarthropathy is the most common form of limited joint mobility syndrome that affects the extremity in T2DM population. The prevalence of stiff hand syndrome varies from 38% to 58% in T1DM subjects and from 45% to 76% in T2DM subjects. Studies documented that the prevalence of stiff hand syndrome increases with the duration of T2DM and also associated with diabetic peripheral neuropathy (DPN). (Pandey et al., 2013) Stiff hand syndrome is considered to be influenced by poor glycemic control although the association between musculoskeletal complications and glycemic control remains controversial. (Silva & Skare, 2012).

A disease with clear similarities to stiff hand syndrome, Dupuytren’s contracture is more common among those with diabetes than in the general population. Dupuytren's contracture results from a thickening, shortening, and fibrosis of the palmar fascia. Flexion contractures of the fingers may result, usually at the fourth finger, but sometimes involving any of the second through fifth digits. The prevalence of Dupuytren’s contracture ranges from 16% to 42% in the diabetic population. (Pandey A et al, 2013) Dupuytren’s contracture has an increasingly well-understood etiology in the absence of diabetes, one that is clearly independent of the glycosylation involved in diabetic complications. This difference, along with a few distinct differences in clinical findings suggests that the pathophysiology of Dupuytren's contracture differs in people with and without diabetes. (Fitzgibbons & Weiss, 2008).
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Carpal tunnel syndrome (CTS) is one of the commonly studied complications in T2DM subjects. The prevalence of CTS in T2DM was found to be between 11-25% being more common in women. (Ebrahimzadeh et al 2013; Pandey et al., 2013; Papanas et al 2010) In advanced cases, atrophy of the thenar muscles and grip strength loss can be seen. However, some authors documented that the real predisposing factor to carpal tunnel syndrome is obesity, common in patients with T2DM. (Geoghegan et al 2004)

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. 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. (Arkkila et al 2003) The prevalence of trigger finger in patients with T2DM ranges from 5% to 36% in those with T1DM or T2DM as compared with 2% in the general population, its development being associated with longer disease duration (Cagliero, Apruzzese, Perlmutter, & Nathan, 2002).

Low back pain is the most common musculoskeletal complication in developing countries and is considered to be a leading cause of work-related disability. Although the exact mechanism of low back pain in T2DM is not well defined, the prevalence is found to be very 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 LBP prevalence of 63.4% among 317 patients with T2DM (Eivazi & Abadi, 2012).
Fatigue is the common symptom among T2DM population. This can be due to the physiological processes and complications associated with long-term T2DM. According to previous studies up to 60% of patients with T2DM experience fatigue symptoms. (Drivsholm, de Fine, Nielsen, & Siersma, 2005) Although numerous lifestyle factors may affect fatigue, being overweight and engaging in low levels of habitual physical activity (PA) have been strongly associated with fatigue and have special clinical relevance for many patients with T2DM.

1.4.2 Foot complications in T2DM

Foot problems are a common complication in people with diabetes. Foot problems most often happen when there is nerve damage, also called neuropathy. This can cause tingling, pain (burning or tingling), or weakness in the foot. It can also cause loss of feeling in the foot. Peripheral neuropathy involves somatic (leading to sensory loss), motor (leading to atrophy of intrinsic foot muscles) and autonomic nerves (leading to loss of perspiration and skin changes). The prevalence of DPN ranges from 7% within 1 year of diagnosis to 50% for those with T2DM duration more than 25 years. If patients with subclinical levels of neuropathic symptoms are included, the prevalence of DPN might exceed 90%.

The high rate of diabetic neuropathy results in substantial morbidity, including recurrent skin complications, lower extremity infections, ulcerations and subsequent amputations. Autonomic neuropathy accounts skin manifestations in T2DM with prevalence ranging from 47.5 - 91.2%. (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 alter the 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’s 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 (Petrofsky, Berk, &
Al-Nakhli, 2012).

Due to loss of sensation on the foot, subjects with DPN presents with increased
plantar pressures superimposing the foot into the very high load. (Abdul et al 2012;
Bacarin, et al 2009; Mickle et al 2011) Murray et al have reported a 57% risk for ulcer
formation at high-pressure points and also in this study they disclosed the relationship
between callus and ulcer locations 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) John et al in 2002 documented that the forefoot is more at risk
for callus formation as compared to the rear foot which depended on the severity of
peripheral neuropathy. In their study they found increased plantar pressure both on the
forefoot and rear foot, whereas the ratio between forefoot and rear foot pressure is
increased in the case of severe peripheral neuropathy. (John & David, 2002) It is well
documented that the forefoot is the common site for increased plantar pressure and calluses
are a risk factor for ulcer formation (Abouaesha et al 2001).
Approximately 15% of T2DM subjects during their lifetime suffer from foot ulceration and it is expected to rise up to 25%. (Singh, Armstrong, & Lipsky, 2005) In the UK and the USA, the prevalence of foot ulceration due to diabetes has found to be 5-7% (Kerr, 2012), whereas in the developing countries it has shown a higher percentage. (Boulton, 2005) In a developing country like India, the prevalence of diabetic foot ulcers was found to be very high. In a study conducted in North India by Shahi et al., it was found that 14% of the T2DM population had foot ulcers. They also found that in the diabetic foot ulcer group 70.10% of the population belonged to rural areas and 29.9% were from the 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).

In India, musculoskeletal and foot complications are under-recognized and requires preventive approach involving T2DM subjects and interdisciplinary team (Fauci et al., 2008). T2DM management, musculoskeletal care, education for patients and their family, implemented screening and risk assessment tools by health providers may have a critical role in the prevention of T2DM related musculoskeletal and foot complications.

1.5 Medical management of T2DM

The epidemic of T2DM and the recognition that achieving specific glycemic goals can substantially reduce morbidity and has made the effective treatment of hyperglycemia a top priority. (Care, 2008; McIntosh A et al., 2001) While the management of hyperglycemia, the hallmark metabolic abnormality associated with T2DM has historically taken center stage in the treatment of diabetes, therapies directed at other coincident features such as, dyslipidemia, hypertension, hypercoagulability, obesity, and insulin
resistance have also been a major focus of research and therapy. (Tan, Polello, & Woodard, 2014) Maintaining glycemic levels as close to the non-diabetic range as possible has been demonstrated to have a powerful beneficial effect on diabetes-specific microvascular complications, including retinopathy, nephropathy and neuropathy. This goal can be achieved not only through pharmacological management but also in combination with lifestyle intervention like physical activity, and diet.

1.5.1 Pharmacological management of T2DM

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 CV risk factors such as lipid profiles.

Metformin is considered to be the first line of therapy to achieve glycemic control in subjects with T2DM. (Harper et al., 2013) 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). Historically the preferred medicine to add as second-line therapy has been a 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. (Bloomgarden., 2007) Insulin is the most effective therapy for lowering glycaemia. Insulins include human insulin and recombinant insulin analogues. (Ganiats., 2006) The insulin analogues currently available include insulin Aspart, Glargine, Detemir, Lispro and Glulisine. Initial therapy is aimed at increasing basal insulin supply, usually with intermediate or long-acting insulin’s. However patients may also require prandial therapy with short or rapid-acting insulin’s. The very rapid-acting and long-acting analogues have not been shown to lower HbA1c more effectively than the older, rapid acting or intermediate acting insulin formulations. A recent Irish study has shown that the prescribing of human insulin is decreasing and that of the insulin analogues is increasing. Insulin therapy is indicated for those, not tolerating oral hypoglycemic therapy, not achieving appropriate glycemic control, being pregnant or planning pregnancy (note that not all analogues are suitable for use in pregnancy) and those with painful neuropathy. In addition to lowering glucose, insulin also has beneficial effects on lipids.

1.6 Lifestyle interventions in T2DM

Lifestyle intervention, in particular, the promotion of weight loss and exercise, is very important in the management of T2DM and has been shown to reduce the HbA1c by up to 2% which is highly significant (MCID for HbA1c is 0.9% with medication in combination with exercise prescription and 0.4% with medication alone) (Susan Manley et al., 2003, Nathan et al., 2009; Harkins V, 2008) Weight loss has positive effects on metabolic control (Nield, L Moore et al., 2009) and cardiovascular risk factors in T2DM. (Fujioka, 2010) Options for healthy eating include simple calorie restriction, reducing fat
intake, consumption of carbohydrates with low glycemic index and restricting the total amount of dietary carbohydrate. Some of the most successful programmes for long-term weight control have included combinations of diet, exercise and lifestyle modification. (Harkins V, 2008) Exercise improves glycemic control even without weight loss and results in reduced body fat content and increased insulin response. (Thomas, Elliott, & Naughton, 2006) Studies have shown that regular physical activity is associated with reduced cardiovascular disease and total mortality in diabetic patients; the reduction in CVD risk associated with the physical activity may be comparable with that of pharmacological treatment prescribed to patients with T2DM (Ryden et al., 2006).

American Diabetes Association (ADA) and the American College of Sports Medicine (ACSM) have recommended 150 minutes per week of aerobic exercises are very effective in controlling blood glucose levels. Studies documented that aerobic exercises lead to glycemic control, the shift towards healthier lifestyle and prevention or modulation of risk factors in cardiovascular disease. There is an increasing emphasis on the accumulation of 150 minutes or more of moderate physical activity/week due to the pooled data from various studies, and moreover, it has become increasingly clear that physical activity is a therapeutic tool in a variety of patients with, or at risk of diabetes and its related complications. Most obese T2DM individuals exhibit a decrease in blood glucose levels after mild-to-moderate exercises. (Colberg et al., 2010; McIntosh A et al., 2001) The magnitude of the decrease in blood glucose levels depends on the duration of the exercise. Blood glucose reduction during physical activity is attributed to attenuation of hepatic glucose production, where the muscle glucose utilization increases normally (Albright et al., 2000). Reduced hepatic glucose production may activate a negative feedback
mechanism to sustain insulin levels during exercise and elevate glucose levels before activity. Mild-to-moderate intensity exercise lowers blood glucose, and this effect is sustained into the post-exercise period. Thus, mild-to-moderate intensity exercise is recommended to facilitate glucose reductions in those with T2DM. Blood glucose response to moderate exercise in lean T2DM individuals is highly variable (Woodward & Feldman, 2013) and is not as predictable as in obese individuals. On the contrary, diet can also plays an important role in lifestyle modifications and forms the cornerstone of the management of blood glucose levels and prevention of other complications like hypertension, higher levels of low-density lipoproteins (LDL) or total cholesterol in the body (Asif, 2014).

Meta-analysis on the use of dietary fibers in T2DM showed beneficial effects of dietary fibers on glycosylated hemoglobin with an overall mean decrease in HbA1c of 0.26% (Post, Mainous, King, & Simpson, 2012) For individuals with T2DM the use of glycemic index and glycemic load may also provide a modest additional benefit for glycemic control over that observed when total carbohydrate is considered alone (ADA, 2008)

1.7 Foot health program in T2DM

Foot problems are a common complication in people with T2DM and can be can be prevented with careful foot care. If complications do occur, daily attention will ensure that they are detected before they become serious. It may take time and effort to build good foot care habits, but self-care is essential. T2DM can lead to many different types of foot complications, including skin infections, calluses, bunions and other foot deformities, or ulcers that can range from a surface wound to a deep infection. These complications can be
prevented through patient structured or comprehensive foot care which consists of education and self-foot care.

Education and knowledge on self-care for patients with T2DM aims to improve their knowledge and skills, enabling them to take control of their condition and to integrate self-management into their daily lives. All the treatment factors, diet, medication, and exercise must be carefully managed on a daily basis by patients. Patients must be able to recognize when they need professional help. Good self-management depends on initial education about the disorder and 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) Several programs are established aiming to educate the diabetes patients to control T2DM 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 patient for optimizing diabetes control and prevention of complications. (Tan et al., 2014)

Whereas, in a lower middle-income country like India, foot is the most ignored part of the diabetes management and there is a dearth of literature on prevalence of diabetic foot and musculoskeletal complications in India. Foot screening is the most ignored part in clinical evaluation of diabetic population. 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.
1.8 Need for the study

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. Diabetes is associated with many complications of which foot complications are considered to have very high prevalence. There is lack of literature regarding the prevalence of diabetic foot complications and musculoskeletal complications in India. Foot screening is the most ignored part in clinical evaluation of diabetic population (Dixit S & Maiya A 2014). 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.

Aim

To estimate the prevalence of musculoskeletal and foot complications in T2DM and to evaluate the effectiveness of structured foot health program on foot biomechanics and quality of life in T2DM.

Objectives

Phase-I

1. To estimate the prevalence of foot and musculoskeletal complications in T2DM.
2. To find the association between foot complications and duration of T2DM.

Phase-II

1. To develop and validate the structured foot health program for T2DM.
2. To assess the effect of structured foot health program on foot biomechanics and quality of life in T2DM.