CHAPTER 1

INTRODUCTION
Non communicable diseases (NCD) are chronic diseases with slower but steady progression causing 38 million deaths per year globally. Diabetes is one of the non-communicable diseases with rising prevalence across the world particularly in developing countries. Global prevalence of diabetes was estimated to be 9% among adults aging more than 18 years. More than 80% of deaths caused by diabetes reported to occur in lower and middle income countries (WorldHealthOrganization 2014a). Diabetes has gained status of epidemic in India with more than 62 million people diagnosed with the disease compared to 31.7 million individuals in year 2000. The incidence of diabetes is expected to increase globally from 171 million in 2000 to 366 million in 2030 with a maximum increase in India.

Increasing prevalence of diabetes in India increases the economic burden by direct expenses borne by the individuals, families and health care systems (Yesudian et al. 2014). The diabetic patients are likely to spend double compared to non diabetic individuals due to higher cost of diabetes management related to complications (Kapur 2001). People with diabetes spend as much as 25% of their monthly income for its management. Cost of medication does contribute to poor compliance to treatment in lower income groups (Odegard & Gray 2008).

Diabetes is a metabolic disorder with multiple etiologies characterized by hyperglycemia (high blood sugars). The most important regulator of uptake of glucose from blood is hormone insulin produced by islet of Langerhands, containing beta cells, which acts on insulin receptors to promote uptake of nutrients by the cells.

Diabetes occurs when the pancreas does not produce enough insulin or when the body is not able to utilize the insulin it produces. The deficient insulin action resulting from inadequate insulin secretion and or diminished tissue response to insulin at one or more pathways of hormone actions is the basis for abnormality, mainly in carbohydrate, and fat metabolism.

Deficiency of insulin results in diminished glucose uptake by cells resulting in hyperglycemia but cells undergo starvation for energy. Along with carbohydrate metabolism fat metabolism is affected as body shifts the energy source from carbohydrate to fat. This results in increase lipolysis, decreased lipogenesis leading to loss of adipose tissues eventually causing weight loss.

Genetic predisposition and epidemiological transition are the risk factors for diabetes. Studies have shown higher risk of diabetes, increased insulin resistance at any given body fat and metabolic abnormalities among Asian Indians than other ethnic groups (Abate & Chandalia 2001). Asian Indians are prone to diabetes even at a lower body Mass Index. Faulty food habits, high fat diets, higher intake of refined foods, decreased physical activity, sedentary nature of occupation, sudden changes in lifestyle due to migration etc are contributing factors in increasing prevalence of diabetes.
Considering the chronic nature of the disease, a constant attention is required for diet, exercise and medication to achieve good glycemic control.

Healthy eating pattern, regular physical activity, stress management and medication are vital components of diabetes management (Franz et al. 2014). Medical management of diabetes involves achieving glycemic targets with oral hypoglycemic agents and or insulin therapy.

Medical nutrition therapy in management of diabetes have been reported to a have strong positive impact and improve glycemic outcome (reduction in Hba1c 0.5 - 2) depending on the duration of diabetes and level of glycemic control. The interventions for improved glycemic control are considered to include reduced energy intake, reduced fat intake, carbohydrate counting and basic nutrition and healthy food choices (Ziemer et al. 2003); (Andrews et al. 2011; Coppell et al. 2010).

Regular physical activity has shown to improve glycemic control in diabetic individuals by improving insulin sensitivity, lowering blood glucose concentration, reduces medication dose, builds muscle mass and improves cardiovascular fitness. A combination of aerobic and resistance exercise have proven to be beneficial in improving metabolic control and overall well being in diabetic patients.

Diabetes can affect nearly every organ/system in the body, initiated from the organ/ system where entry of glucose is independent of insulin. For e.g. nervous system including eyes, medullary part of Kidney etc (Alberti & Zimmet 1998).

The complications of diabetes can be traditionally divided into two categories: microvascular and macrovascular complications. Microvascular complications refer to changes in smaller blood vessels including the eyes (Diabetes retinopathy), kidneys (Diabetes nephropathy) and nerves (Diabetes neuropathy). Macrovascular complications refer to changes in moderate to large blood vessels such as brain (Cerebrovascular diseases), heart (Cardiovascular diseases) and periphery (Peripheral vascular diseases). Both macrovascular and microvascular complications cause significant morbidity and mortality among long standing diabetic subjects (Zargar et al. 1999).

Diabetes is the leading cause of renal failure in both developed and developing countries. Among the elderly population, Diabetes is the leading cause of not less than 46% of Chronic Kidney diseases (Prakash et al. 2006). Diabetes retinopathy is highest among Indians. Ulceration of foot or amputation is significant causes of morbidity in diabetic subjects. The incidence of amputations of lower limb are seen 10 time more in diabetic patients compared to non-diabetic population in developed countries (Icks et al. 2011).
Patients with diabetes may have negative impact on psychological well-being (Gask et al. 2011; Robertson et al. 2012). Higher proportions of subjects with diabetes are likely to have depression (14%) and increased diabetes-related distress (45%). Factors worsening the psychological well-being include, presence of complications, hypoglycemia, using insulin or medications, perceived burden of diabetes, conflicts in family and feeling of discrimination (Nicolucci et al. 2013).

Very recently oxidative stress due to accumulation of reactive oxygen species has been identified to be the basic causative factor for the diabetic condition including insulin resistance, beta cell dysfunction and impaired glucose tolerance eventually leading to diabetes mellitus. Reactive oxygen species are generated as a byproduct of normal metabolism in aerobic organisms. Pollution, smoking, exposure to ultra violet rays are external sources whereas mitochondria, enzymes like xanthine oxidase, NADPH oxidase are internal sources of reactive oxygen species. Presence of unpaired electrons in reactive oxygen species makes these free radicals highly reactive and capable of initiating lipid, protein and DNA oxidation. It has been reported that reactive oxygen species can reduce glucose stimulated insulin secretion, decreased gene expression of β cells and induce cell death (Simmons 2006). Oxidative stress results when the production of reactive oxygen species and its intermediates exceeds the antioxidant defense system’s efficiency to neutralize and eliminate them.

Chronic hyperglycemia in diabetes mellitus increases generation of reactive oxygen species (ROS) from various metabolic pathways like glucose auto-oxidation, increased polyol pathway, activation of protein kinase C and synthesis of advanced glycation end products etc. (Fernández-Mejía 2013; Giacco & Brownlee 2010; Johansen et al. 2005). With low level of antioxidative enzyme expression and high oxidative energy requirement, chronic oxidative stress can have negative impact on β cells of the pancreas (Evans et al. 2003; Shah et al. 2007b).

The increase in the level of ROS in diabetes could be due to their increased production and/or decreased destruction by nonenzymic and enzymic antioxidants forming endogenous and exogenous defense system of our body.

Malondialdehyde is the marker of lipid peroxidation indicating the level of oxidative stress (Hu et al. 2006). The endogenous enzyme system consists of enzyme superoxide dismutase; glutathione peroxidase and catalase convert the free radicals to water and less reactive substance.

Along with these enzymes, dietary antioxidants such as beta carotene, vitamin C, E and selenium work synergistically scavenge the free radicals. Oxidative stress markers are shown to be lowered with increased intake of antioxidant rich food like fruits and vegetable in diabetic subjects (Asgard et
al. 2007). However, consumption of fruits and vegetables is found to be less in Indian subjects (Sachdeva et al. 2014).

The level of these antioxidant enzymes and nonenzymic antioxidants reduce the free radicals and critically influence the susceptibility of various tissues to oxidative stress and associated development of diabetes and related complications (Maritim et al. 2003).

Lifestyle factors such as physical inactivity, faulty dietary habits, obesity etc, the established risk factors for diabetes have shown to increase oxidative stress. Oxidative stress, lifestyle factors and diabetes are closely related to each other and oxidative stress is found to be negatively related to body antioxidative enzymes (Olusi 2002).

The amount of carbohydrate in a meal, dietary fiber and available insulin is major determinant of postprandial glycemic response. Monitoring carbohydrate intake by carbohydrate counting or by estimated carbohydrate intake is the fundamental approach towards achieving glycemic control. Similarly, substituting foods having higher glycemic load for lower glycemic load has shown to improve glycemic control (AmericanDiabetesAssociation 2008).

However, diabetes management has never been emphasized on its root cause or strengthening antioxidant system by improving dietary antioxidant intake. It is important to assess the oxidative stress and antioxidative enzyme status in diabetes subjects with and without microvascular complications. The relation of oxidative stress, antioxidant enzyme pattern, dietary antioxidant intake, lifestyle pattern, diabetes related distress of diabetic individuals needs to be explored.

Thus, the present study aims to assess antioxidative status of subjects with diabetes, with or without microvascular complication along with diet, lifestyle and stress related factors with following objectives.

**Broad Objectives**

- To assess lifestyle, diet history, diabetes related stress, physical activity level of patients with type 2 diabetes mellitus
- To assess antioxidative status in a subset diabetes subjects with and without complications

**Specific objectives**

- To assess anthropometric status relating to metabolic disorders
- To assess current dietary pattern to know the awareness of diabetic people regarding the importance of antioxidant rich food
• To assess physical activity pattern among the subjects to know the awareness levels of diabetic people regarding the importance of Physical activity
• To evaluate diabetes related distress in the subjects
• To study factors affecting diabetes distress
• To assess medical and dietary compliance among subjects
• To study other lifestyle related factors like alcohol, tobacco consumption and smoking
• To assess and compare oxidative stress and antioxidative enzyme status in subjects with and without microvascular complications of diabetes and paired controls
• To assess interrelation of different antioxidative enzymes in different clinical conditions
• To study factors affecting oxidative stress in diabetic subjects, with or without complications.