Chapter-1

Introduction
Section-I

Diabetes mellitus
DIABETES MELLITUS

Introduction

The economic growth and development of the past three decades have been dramatic. However, economic development has set the scene for the transformation of lifestyles, eating habits, and traditional societal and family structure. Lifestyle related non-communicable health conditions are having an increasingly negative impact on the health of many adults and children. Type 2 diabetes mellitus (T2DM), which is linked both directly and indirectly to behavioural, nutritional and environmental factors, has emerged in recent years as the leading cause of illness, disability and death. Over the past two decades, the incidence of T2DM in adolescents and children has markedly increased and it accounts for as many as one third of all the new cases of diabetes diagnosed in adolescents. Type 2 diabetes is one of the major public health challenges of the 21st century. The prevalence of type 2 diabetes is rising relentlessly around the world. Current estimates suggest that globally, the number of persons with diabetes will rise from 151 million in the year 2000 to 221 million by the year 2010 and to 300 million by 2025. This rise is predicted to occur virtually in every nation, with the greatest increase expected in developing countries. This explosive increase in the prevalence of type 2 diabetes and the consequences of its complications and associated disorders represents the greatest health care challenge facing the world today (P Zimmet, 2003).

Diabetes prevalence is currently estimated at 6.2% in the developed world, and forecast to rise to 7.6% by 2025. Developing countries are starting from a lower baseline, at 3.5%, but is set to increase by more than a third to 4.9%, in 2025 (King et al., 1998). This translates into an increase of nearly 6 million patients every year, according to statistics from the Centre for
Disease Control (CDC), South East Asian countries have the highest burden of diabetes (A. Hussain et al., 2007). The global prevalence of Diabetes Mellitus (DM) was estimated to be 4.0% in 1995 and projected to rise to 5.4% by the year 2025. A major part of this increase is expected to occur in developing countries. It has been projected that the numbers will increase by 42% (from 51 to 72 million) in developed countries and by 170% (from 84 to 228 million) in developing countries. Most of the subjects with DM are expected to be 45 to 64 years of age in developing countries and >65 years of age in developed countries. This pattern may change considerably by the year 2025, given the recent evidence of increasing DM among obese children and adolescents (Rajeev Gupta & Praneet Kumar, 2007). Diabetes Mellitus is one of the fastest growing chronic diseases in the world. India is regarded as the “diabetes capital of the world,” with an estimated 46 million people with diabetes. By the year 2030, the number is expected to climb to 80 million.

**Undiagnosed Diabetes – The Hidden Danger**

Patients diagnosed with diabetes represent the tip of the iceberg, and a large number of patients with undiagnosed diabetes may also be at risk of adverse clinical outcomes. In the AUSDiab study, there was one undiagnosed case for every known case of diabetes (Dunston DW et al., 2002). An observational study carried out in an apparently healthy, elderly (70-79 years) population in the US revealed that 8% of the 3,075 participants had undiagnosed diabetes. A study in UK, which surveyed 553 subjects without known diabetes in an impoverished urban area, illustrates how genetic and socioeconomic factors combine to amplify the problem of undiagnosed diabetes (Riste L et al., 2001). Diabetes mellitus exhibits iceberg phenomenon, where the unknown morbidity exceeds the known morbidity. It is important to note that the studies that have shown an increase in prevalence of diabetes have also reported a very high
prevalence of undiagnosed diabetes in the community. In the Chennai Urban Rural Epidemiology Study (CURES), the prevalence of known diabetes was 6.1 percent and that of undiagnosed diabetes was 9.1 percent (Mohan V et al., 2006). Similarly, in Amrita Diabetes and Endocrine Population Survey (ADEPS), the prevalence of known and undiagnosed diabetes was 9.0 and 10.5 percent respectively (Sicree R et al., 2006). The Kashmir valley study showed that the prevalence of undiagnosed diabetes was 4.25 percent, which was more than double to that of the known diabetes (1.9%) (Zargar AH et al., 2000). The individual who are unaware of their disease status are left untreated and are thus more prone to microvascular as well as macrovascular complications. **Hence, it is necessary to detect the large pool of undiagnosed diabetic subjects in India and offer early therapy to these individuals.**

**The Burden of Type 2 Diabetes**

A diagnosis of diabetes has a profound impact on the life expectancy, and a patient diagnosed with type 2 diabetes in the middle age (40-49 years) stands to lose as much as 10 years of life expectancy. Given the close association between type 2 diabetes and the cardiovascular risk factors constituting the dysmetabolic syndrome, it is not surprising that most type 2 diabetic patients ultimately die from a cardiovascular cause (Zimmet, 2003). When compared to non diabetic subjects, diabetic patients are at a three (men) to six fold (women) increased risk of suffering myocardial infarction and coronary heart disease is the main cause of death in this population (A. M. Wagner et al., 2002). Both the risk of having and dying from the stroke is three fold higher when diabetic patients are matched with their non diabetic controls. Diabetic patients most frequently suffer from occlusive strokes in the territory of the small paramedian penetrating arteries arising from the circle of Willis (Aoron Vinik, 2002). Diabetic retinopathy is estimated to account for 5% of all cases of blindness globally; upto 50% of patients receiving
renal replacement therapy (RRT) have diabetic neuropathy (Nish Chaturvedi, 2007). Diabetes is the commonest cause of leg amputations worldwide and it poses a 13-fold risk increase. Each year 5% of patients with diabetes will develop a foot ulcer, the lifetime risk being 15% (Clifford P Shearman, 2010).

**Burden of Diabetes Related Complications in India**

Diabetes is now considered as a vascular disease. Diabetes affects large blood vessels (cardiac, cerebral and peripheral arteries) small vessels (kidney and retina), nerves and other organs. Both macrovascular and microvascular complications cause significant morbidity and mortality among diabetic subjects (Zargar AH et al., 1997).

Diabetes can affect nearly every organ system in the body; it can cause blindness, end stage renal disease, lower extremity amputations, and increased risk of stroke, ischemic heart disease, peripheral vascular disease and neuropathy. This is causing great concern since the cost of treating diabetes complications is becoming a serious drain on health resources. In the United States, diabetic retinopathy, nephropathy and neuropathy account for almost 50% of the total costs of complications resulting from type 2 diabetes (Aniz Girach et al., 2006).

In type 2 diabetes mellitus the risk of some of these complications (eg. coronary artery disease), may start even before the onset of diabetes. Diabetics are 25 times more likely to develop blindness, 17 times more likely to develop kidney disease, 30 - 40 times more likely to undergo a major amputation, 2- 4 times chances of developing myocardial infarction and two times chance of getting stroke (Sanger TJ, 1995). World Health Organisation in 1997 estimated that about 1, 02, 000 persons died of diabetes mellitus in India. Life expectancy in people with
diabetes might be shortened by as much as 15 years (Donnelly R et al., 2000). Considering these facts health problems associated with diabetes mellitus are a growing source of concern in India.

**Complications of Diabetes Mellitus**

**Acute Complications**

**Diabetic ketoacidosis:**

Diabetic ketoacidosis (DKA) is one of the major acute diabetic complications. It usually occurs in the context of total insulin deficiency, such as insulin dependent diabetes mellitus (IDDM). It occurs rarely in non insulin dependent diabetes mellitus (NIDDM) under the stress of acute illness. DKA is clinically defined by absolute insulin deficiency with severe hyperglycemia (glucose levels usually more than 400 mg/dL), increased lipolysis, increased ketone production, hyperketonemia (ketone levels positive at 1: 4 dilution of serum or greater or beta hydroxybutyrate more than 0.5 mmol/L), and acidosis (pH ≤ 7.3 or bicarbonate ≤ 15 mEq/L). The mortality rate for ketoacidosis ranges from 2% - 5% in developed countries and 6%-24% in developing countries (Keller, 1986; Hamblin et al., 1989; Wetherhall et al., 1992). The most common causes of ketoacidosis are infections (30%), non-compliance with treatment (20%) and newly diagnosed diabetes (25%). Above one quarter of cases have no precipitating event (Powers, 2001).

**Hyperosmolar non–ketotic coma:**

Hyperosmolar non-ketotic coma (HNC) is clinically defined by the presence of relative insulin deficiency and hyperglycemia, usually more than 1000 mg/dL with associated elevated serum osmolality (300 mOsm/kg), dehydration, and stupor, progressing to coma if uncorrected, without the presence of ketosis or acidosis. These patients have sufficient circulating insulin to prevent lipolysis and ketosis. Unfortunately, there are no population based studies for HNC. It
occurs rarely and is clinically associated with NIDDM. Typically, in clinical practice, HNC is seen in patients with NIDDM and residual insulin secretion. HNC is reported to occur more often in Caucasian females (Siperstein, 1992). The usual precipitating factors are dehydration, medications such as steroids and thiazides, acute illness, cerebral vascular disease, advanced age, and rarely new diagnosis of diabetes. Mortality attributed to HNC is variable with rates from 10%-15%, most likely depending on the underlying illness or co-morbidity (Arieff & Carrol, 1972; Small et al., 1988).

**Lactic acidosis:**

Lactic acidosis (LA) has the poorest prognosis among all the acute metabolic complications of diabetes. Lactic acidosis consists of elevated lactic acid (lactic acidemia, \( \geq 2.0 \) mmol/L) with acidosis (pH\( \leq 7.3 \)) and without ketoacidosis. There may be low levels of ketones present (\( \leq 1:4 \) on serum dilution, or beta hydroxybutyrate >0.4 but <0.6 mmol/L). Approximately half of the reported cases of LA had occurred in patients with diabetes (Kriesberg, 1980). Currently, LA is rarely seen in diabetic patients, particularly since the withdrawal of phenformin from the market. Most LA occurred in individuals aged more than 45 years, in women and in Caucasians. The usual precipitating factors for LA are hypoxia and some medications such as phenformin. The mortality rate with LA is high. Higher the lactic acid level with acidosis, higher the mortality rate (Powers, 2001).

**Hypoglycaemia:**

Hypoglycaemia is common in insulin treated diabetic patients and also occurs occasionally in patients treated with the oral hypoglycaemic sulfonylurea agents. Hypoglycaemia may range from very mild lowering of glycaemia (60 – 70 mg/dL) with minimal or no symptoms,
to severe hypoglycaemia with very low levels of glucose (<40 mg/dL) and neurologic impairment.

The major morbidity associated with hypoglycaemia is temporary neurologic deficit and coma, seizures with central nervous system injury, and permanent neurologic impairment if treatment is delayed or omitted. Deaths related to hypoglycaemia in diabetes occur rarely. Among patients using insulin pump therapy, the majority of patients with hypoglycaemia survive the episode (Teutsch et al., 1994).

Chronic Complications of Diabetes Mellitus

1. Microvascular complications: Retinopathy, neuropathy and nephropathy
2. Macro vascular complications: Coronary artery disease, peripheral vascular disease, cerebrovascular disease
3. Diabetic cardiomyopathy
Other complications

1. Gastrointestinal complications like gastro paresis, diarrhoea.
2. Genitourinary complications like uropathy, sexual dysfunction
3. Dermatological complications

Microvascular Complications

The risk of chronic complications increases as a function of duration of hyperglycaemia. They usually become apparent in the second decade of hyperglycaemia. Since type 2 diabetes may have a long asymptomatic period of hyperglycaemia, many individuals with type 2 diabetes have complications at the time of diagnosis.

Randomized, prospective clinical trials involving large numbers of individuals with type 1 or type 2 diabetes has conclusively demonstrated that a reduction in chronic hyperglycaemia prevents or reduces retinopathy, neuropathy, and nephropathy (The DCCT research group, 1993; UK prospective diabetes study group, 1998). Other incompletely defined factors also modulate the development of complications. For example, despite of longstanding diabetes mellitus, some individuals never develop nephropathy or retinopathy. Many of these patients have glycemic control that is indistinguishable from those who develop microvascular complications. Because of these observations, it is suspected that a genetic susceptibility for developing particular complications exists. However, the genetic loci responsible for these susceptibilities have not been identified yet (Powers AC, 2001).
Diabetic retinopathy

Diabetic retinopathy is the most specific of all diabetic complications and is one of the leading causes of blindness. There are very few studies from India which has looked at diabetic retinopathy prevalence. In 1996, Rema et al., observed the prevalence of diabetic retinopathy in a clinic based study to be 34.1%. Dandona et al., had reported a prevalence of 22.6% in an urban south Indian population (Hyderabad) in the year 1999. Narendran et al., 2002, reported a higher prevalence of 26.8% in self reported diabetic subjects in Palakkad in Kerala state. The Chennai Urban Rural Epidemiology Study (CURES) Eye Study-1 is the largest population based data on the prevalence of diabetic retinopathy. This study reported a prevalence of 17.6% (Rema M et al., 2005).

Diabetic nephropathy

A few studies have looked at the prevalence of diabetic nephropathy in India. But most of these are clinic based reports. John L et al., 1991, reported that the prevalence of microalbuminuria was 19.7% and diabetic nephropathy was 8.9%. Gupta DK et al., 1991, found that the prevalence of microalbuminuria was 26.6%. A study from Pune showed a prevalence of microalbuminuria to be 23% (Yajnik CS et al., 1992). Vijay V et al., 1994, reported a prevalence of 18.7% of proteinuria in a clinic based study from Chennai. The first population based prevalence of diabetic nephropathy in India was reported by Unnikrishna RI et al., in 2007. In this study the prevalence of overt nephropathy was found to be 2.2% and that of microalbuminuria was 26.9%.
Diabetic neuropathy

The prevalence of neuropathy was found to be 27.5% (Ashok S et al., 2002) and 19.1% (Ramachandran A et al., 1999) in two separate clinic based studies from Chennai. A recent study reported a high prevalence of 29% of neuropathy in newly diagnosed diabetic subjects (Dutta A et al., 2005). Very recently, population based data from CURES was published which showed that the prevalence of neuropathy in urban population was 26.1% (Pradeepa R et al., 2008). A recent report showed that foot ulcers were more common among diabetic subjects in the rural area compared to their urban counterparts (Viswanathan V et al., 2006). They also found that the rates of amputations were higher in rural area compared to urban area.

Societal Burden of Diabetes

The progression of diabetes demands high levels of medical care, and the management of patients is inevitably costly. The cost of the diabetes care is high and is escalating worldwide. In 2007, the world spent an estimated 215-375 billion USD for diabetes care. It is likely to rise from 234 to 411 billion in the next 20 years. The major brunt will be borne by the developing countries (Ramachandran Ambady et al., 2008). It is well established that the hospital costs of the complications is the overriding cost factor. The Cost of Diabetes in Europe Type-2 Study (CODE-2) reported that 72% of the patients had at least one complication, of which a third had macrovascular disease. The cost of care was up to 250% higher in people with complications compared to those without complications. Diabetes also has significant effect on the person and their family. Lost production caused by sickness, absence from work, early retirement and premature mortality carry high costs to the public purse. 80% of the world’s diabetics reside in lower income nations, posing an even greater burden on developing economies. People with
diabetes had medical expenditures some 2.4 fold higher than expenditure incurred by matched population without diabetes. The loss of earnings experienced by type 2 diabetes patients and their carers was significant, and a strong association was found between patients’ loss of earnings and the presence of complications. There are economic reasons together with human factors for seeking to reduce or delay the complications of diabetes (Julia Bottomley, 2008).

Economic Burden of Diabetes Mellitus in India

Diabetes is becoming one of the major public health problems, because a great proportion of the healthcare expenditure has been spent on the treatment of its associated morbidity and mortality. The developing countries such as India bear the highest burden from diabetes and its complications. The expected increase in the number of subjects with diabetes will have serious impact on the country’s health care system. The World Bank estimate in 2000 showed that diabetes accounted for 1,870,000 Disability Adjusted Life years in India, with a per capita health care expenditure of $ 21 (Ramachandran Ambady et al., 2008). Despite diabetes being a lifelong disorder and is expensive to manage, there is lack of data on its economic burden in India. In India the direct medical cost to identify one subject with insulin glucose tolerance is INR 5,278 (Ramchandran A et al., 2007). The cost of insulin amounts to 350 USD (16,000 Indian rupees) per year, while medication for non insulin requiring patients costs about 70 USD per year (Ramachandran A and Shobhana R, 2007).

A recent study in India showed a two fold increase in expenditure on diabetes care in urban areas from 1998-2005. The median expenditure had risen from INR 4200/- (USD 95) to INR 9000/- (USD 203) (Ramachandran A et al., 2007).
In 2000, a study done by Shobhana. R et al., found that treatment of diabetes becomes more expensive as disease duration increases. One more recent study concluded that a majority of diabetes patients spend a significant proportion of their family income on diabetes related expenditure (Rs 6000 or USD 150) per year (Kumar et al., 2008). The indirect cost is more difficult to assess and much higher than the direct cost. The proportion of annual income spent on health care is around 25-30% by the poor people. It has also been shown that cost increases many fold in the presence of complications (Ramachandran Ambady et al., 2008).

**Causes for the Rise in Prevalence of Diabetes in India**

**Genetic predisposition**

Several studies on migrant Indians across the globe have shown that Asian Indians have an increased risk for developing type 2 diabetes and related metabolic abnormalities compared to the other ethnic groups. Although the exact reasons are still not clear, certain unique clinical and biochemical characteristics of this ethnic group collectively called as the “Asian Indian phenotype” is considered to be one of the major factors contributing to the increased predilection towards diabetes. Despite having lower prevalence of obesity as defined by body mass index (BMI), Asian Indians tend to have greater waist circumference and waist to hip ratio and thus having a greater degree of central obesity. Asian Indians have more total abdominal and visceral fat for any given BMI and for any given body fat they have increased insulin resistance (Mohan V et al., 2006).

Since 2007, Genome wide association studies has catalogued around 20 genes (like TCF7L2, HHEX, CDKAL1, SLC30A8 etc.) showing a strong association (with modest odds ratio ranges 1.2 to 1.5) with type 2 diabetes mellitus (Sladek et al., 2007; Laura J. Scott et al., 2007;
Eleftheria Zeggini et al., 2007). All these factors suggest that Asian Indians are more prone to diabetes and related metabolic abnormalities.

**The epidemiological transition**

The dramatic rise in the prevalence of type 2 diabetes and related disorders like obesity, hypertension and the metabolic syndrome could be related to the rapid changes in lifestyle that has occurred during the last 50 years. Although this “epidemiological transition” which includes improved nutrition, better hygiene, control of many communicable diseases and improved access to quality healthcare have resulted in increased longevity, it has also led to the rapid rise of the new age diseases like obesity, diabetes and heart disease. The intrusion of western culture into the lives of traditional indigenous communities had also has devastating results in terms of the rise in diabetes and related metabolic disorders (V. Mohan et al., 2007).

**Accessibility and affordability of high calorie food and physical inactivity**

The ‘fast food culture’ which has overwhelmed in towns and villages is also a major driver of the diabetes epidemic (Mohan V et al., 2007). The ‘fast-foods’ that are fat and calorie rich are easily available in the numerous food joints. One point worth emphasizing is that diabetes can no longer be considered as a disease of the rich. The prevalence of diabetes is now rapidly increasing among the poor in the urban slum dwellers, the middle class and in the rural areas. This is due to rapid changes in physical activity and dietary habits even among the economically backward sections of the society. Unfortunately the poor diabetic subjects delay taking treatment leading to increased risk of complications. Moreover, as the epidemic matures and reaches the next stage of transition, the rich and affluent will rapidly change their activity patterns and start making healthier food choices and ultimately the diabetes and heart disease will decrease in this section of the society. This has been demonstrated in the developed world where
the prevalence of diabetes and cardiovascular diseases are higher among the lower socioeconomic group and in rural areas compared to higher socioeconomic group and urban areas. The next factor driving the epidemic is the adoption of sedentary behaviour. Over the past few decades, a huge number of the working population has shifted from manual labour associated with the agriculture sector to physically less demanding office jobs. With the advent of computers, video games and improved transport facilities is now affecting the children and youth. All these factors will decrease physical activity and lead to obesity. It was observed that the prevalence of diabetes was almost three times higher in individuals with light physical activity compared to those having heavy physical activity. In addition to above factors servant maid culture in upper class society women and children is also a reason for obesity, especially in India (Misra A et al., 2001).

**Television**

The advances in technology that accompany economic development further reduce the need and opportunity for physical activity. Television exposes children and adults to hours of commercials for nutritionally poor foods. A typical child watches approximately 40,000 commercials on television each year. Television viewing among children is correlated with a higher intake of nutritionally poor foods and lower intake of fruits and vegetables (L.D.Ritchie et al., 2005). Prolonged TV watching is associated with significantly elevated risk of obesity and type 2 diabetes in females (Frank B. Hu et al., 2003).

**Cell phones, cars and video games**

With the advent of highly addictive computer and video games, sedentarism is now affecting the children and youth as they tend to spend more time in front of television sets or computers than playing outdoors. All these things directly or indirectly prolong sedentary time and some video games have even impact on psychological stress (Mohan V et al., 2005).
Environmental pollutants

Persistent organic pollutants are organic materials that are persistent and largely distributed in the environment, having bio accumulative properties and are toxic to humans and wildlife. Even though little attention was received about the role of persistent organic pollutants (POPs) in diabetes prevalence, in recent years many studies showed a strong association between POPs serum concentration and diabetes (Lee DH et al., 2006; Rignell-Hydbom A et al., 2009). One of the most investigated POPs related to adverse effects on glucose and lipid metabolism is the extremely toxic 2, 3,7,8-tetrachlorodibenzo-p-dioxin (TCDD). Decline of glucose uptake by adipose tissue, liver and pancreas accompanied by reduced insulin production and secretion by the pancreatic beta cells are most reported effects (T.L.M. Hectors et al., 2011).

Nuclear families and small families

In recent years, number of nuclear families is increasing and this is showing impact on children food habits and physical activity. In joint families there used to be more children to play and elders used to take care of their food habits. But now only one or two kids, pampering is more, both parents are working; they have no time to supervise their children’s activities. Due to these factors children are getting habituated to TV watching or video gaming and limit to less unhealthy food eating which finally leads to early onset of lifestyle diseases (Temple et al., 2007).

Hence early identification of the risk factors associated with diabetes and appropriate interventions aimed at preventing the onset of diabetes and its complications are urgently required in all age groups.
Diabetes has reached an epidemic magnitude in many countries, and more so in developing countries, causing a great burden from life threatening complications of varied nature. The rising tide of type 2 diabetes and its complications will place an increasingly heavy burden of morbidity and mortality on patients and their families for decades to come. The expenditure required to manage these patients will stretch the healthcare systems even of the richest countries, ample evidences are from many long term prospective studies DCCT, UKPDS, Steno, Kumamoto (Gaede P et al., 1999). Current predictions are that management of people with diabetes and its associated complications will be a major challenge to the developing world over the next 25 years. In developing countries more than 50% of diabetics remain undiagnosed. Many do not seek medical help until debilitating complications force them to do so. This is particularly important for those young people who are at risk for developing diabetes, as they will have to live with the complications of the disease for longer than patients who develop diabetes later in life (Nish Chaturvedi et al., 2007). With the increase in prevalence of type 2 diabetes mellitus in adolescents, a rise in incidence of secondary co-morbidities including hypertension, hyperlipidemia, nephropathy, and retinopathy is anticipated. Furthermore, findings of studies in young adults have suggested that the development and progression of clinical complications might be especially rapid when the onset of type 2 diabetes is early, raising the possibility of a serious public health challenge in the next few decades. Occurrence of type 2 diabetes during adolescence seems to place the individual at increased risk of morbidity and mortality during the most productive years of life (Orit Pinhas-Hamiel et al., 2007). Recent reports suggest an incidence of 8% to 45% of type 2 diabetes among children newly diagnosed with the disease, compared with 1% to 2% in previous reports (Samy I. McFarlane et al., 2003). A substantial 80% increase will be seen in middle to low income countries and the highest rise will be seen in the
Indian sub-continent (Nitin Gholap et al., 2011). The pandemic of diabetes, along with its high human and economic costs, is showing no signs of reduction and therefore, new approaches are urgently needed to prevent, slow the progression and limit the consequence of the disease.

**Strategies to Prevent or Delay the Onset of Diabetes**

Type 2 diabetes is a global crisis that threatens the health and economy of all the nations, particularly in developing countries. This epidemic is primarily driven by rapid urbanization, nutrition transition, and increasing sedentary lifestyles. When type 2 diabetes has become manifest, it is most often too late to reverse the glucotoxic effects of hyperglycemia on beta cell function. By the time the diagnosis of diabetes is made, diabetes related tissue damage occurs in nearly half of the patients. Even after the diagnosis, the glycemic control is suboptimal in more than 50% of people, leading to the vascular complications. Evidences suggest that early detection of diabetes by appropriate screening methods, especially in subjects with high risk for diabetes will help to prevent or delay complications and thus reduce the clinical, social and economic burden of the disease. Given the magnitude of the problem, interventions to delay or even prevent the development of type 2 diabetes mellitus therefore seems to be more important than treatment, regarding population health and the burden of healthcare costs. The purpose of screening is to identify asymptomatic individuals who are likely to have diabetes.
Section-II

The Concept of Prediabetes
THE CONCEPT OF PREDIABETES

Introduction

The prevalence of obesity and diabetes is increasing worldwide. Patients with overt diabetes are often asymptomatic despite of very high blood glucose levels. Early detection of diabetes would be a very important step leading to measures to reduce the risk of heart disease, along with controlling the other risk factors such as lowering cholesterol, and also reducing high blood pressure. Epidemiologic evidence suggests that the complications of diabetes begin early in the progression from normal glucose tolerance to frank diabetes. Early identification and treatment of persons with prediabetes have the potential to reduce or delay the progression to diabetes and related cardiovascular disease and microvascular disease (Morali D. Sharma, 2009). Prediabetes is a condition where a person has a blood sugar level higher than normal, but not high enough for a diagnosis of diabetes. He or she is at higher risk for developing type 2 diabetes and other serious health problems, including heart disease, and stroke. The term prediabetes refers to subjects with impaired fasting glucose and/or impaired glucose tolerance who are at increased risk for type 2 diabetes mellitus. Although both types of subjects are at increased for developing type 2 diabetes mellitus and cardiovascular disease, they manifest distinct metabolic abnormalities. The global prevalence of prediabetes has been increasing progressively in the past few decades; currently prediabetes is not regarded as an independent clinical entity but only as a risk factor for others. All forms of diabetes pass through prediabetic state before transforming into complex diabetes. Similar to DM, fasting plasma glucose (FPG) and oral glucose tolerance tests (OGTT) are both used independently as defining criteria for Prediabetes (Sang Youl Rhee & Jeong-Taek Woo, 2011). Recently hemoglobin A1c (HbA1c) is also being used in the screening of prediabetes (American Diabetes Association, 2010).
Epidemiology of Prediabetes

According to several epidemiological studies the worldwide prevalence of prediabetes exceeds that of true diabetes. International Diabetes Federation stated that in many parts of the world the IFG prevalence was 2.0 to 17.3% (Unwin N et al., 2002). In 2010, the worldwide estimation for IGT according to IDF Diabetes Atlas is 340 million (Unwin N et al., 2010). North America has the highest prevalence of IGT in the world with 10.4%, Europe 8.7%, Middle East 8.2%, South East Asia 6.2% and Western Pacific Region 7.7% respectively. By 2030, the rise in IGT prevalence would reach 8.4% which will be approximately 462 million people (Abdul-Ghani MA et al., 2008). The National Urban Diabetes Survey conducted in six major cities from different parts of India concluded the prevalence of IGT was higher than that of type 2 diabetes in four out of six cities studied. The prevalence of IGT was 16.8% in Chennai, 14.9% in Bengaluru (formerly Bangalore), 29.8% in Hyderabad, 10% in Kolkata, 10.8% in Mumbai and 8.6% in New Delhi (Ramachandran A et al., 2001). The ADEPS done in Kerala showed that 11.2% of the subjects had either IFG or IGT (Menon VU et al., 2006). Projections for the whole of India would be 62.4 million people with diabetes and 77.2 million people with prediabetes according to a survey conducted by Indian Council of Medical Research-India Diabetes study (Anjana RM et al., 2011).

Diagnostic criteria for Prediabetes

The development of type 2 diabetes mellitus is known to proceed over many years with gradual decompensation from normal glucose homeostasis to overt diabetes mellitus. Two asymptomatic prediabetic stages can be identified: Impaired Fasting Glucose (IFG) and Impaired
Glucose Tolerance (IGT), both with varying degrees of insulin resistance with accompanying compensatory increased insulin production followed by β-cell insufficiency and falling insulin levels. IGT was introduced in 1979 and defined by World Health Organization (WHO) in 1980. IFG was introduced by ADA in 1997 and was defined by the WHO in 1991. In 2004, ADA suggested changing the lower limit from 6.1mmol/L to 5.6mmol/L. This new wider IFG definition has not been accepted by the WHO. In the present study only WHO 1999 criteria was used.

**Diabetes mellitus**

- **Fasting plasma glucose concentration** ≥126 mg/dl or ≥7.0 mmol/L
- **2- Hour post glucose** ≥200 mg/dl or ≥11.1 mmol/L

**Impaired fasting glucose**

- **Fasting plasma glucose concentration** 110-125 mg/dl or 5.6-6.9 mmol/L (WHO)
- **2- Hour post glucose** <140 mg/dl or <7.8 mmol/L
- **Fasting plasma glucose concentration** 100-125 mg/dl or 5.6-6.9 mmol/L (ADA)

**Impaired glucose tolerance**

- **Fasting plasma glucose concentration** <126 mg/dl or <7.0 mmol/L
- **2- Hour post glucose** 140-199 mg/dl or 7.8-11.0 mmol/L

Recently, the International Expert Committee recommended that HbA1c be added to the diagnosis of DM of over 6.5%, and an HbA1c between 5.7 and 6.4% as **prediabetes**.

**Risk Factors for prediabetes**

- Body mass index ≥ 25 kg/m²
- Physical inactivity
- First degree relative with type 2 diabetes mellitus
- High risk race/ethnicity (e.g., African American, Latino, Native American, Asian American, Pacific Islander)
- Women who delivered a baby weighing > 9 lb
- Women who were diagnosed with gestational diabetes
- Hypertension (≥ 140/90 mm Hg or on therapy for hypertension)
- High-density lipoprotein cholesterol <35 mg/dl and or triglycerides > 250 mg/dl
- Women with polycystic ovarian syndrome
- Hemoglobin A1c ≥5.7%, impaired oral glucose tolerance, or impaired fasting glucose on previous testing
- Other clinical conditions associated with insulin resistance (e.g., severe obesity, acanthosis nigricans)
- History of cardiovascular disease

**Pathophysiology of Prediabetes**

The two most important factors that would explain the pathophysiology of prediabetes are increased insulin resistance and decreased insulin secretion. There are distinguishable characteristics between the subtypes in isolated IFG and IGT subjects after analyzing the patterns of insulin resistance and insulin secretion (Sang Youl Rhee & Jeong-Taek Woo, 2011).

**Insulin Resistance in Prediabetes**

Increased state of insulin resistance is a marker for elevated levels of fasting plasma insulin concentration in prediabetic subjects. Insulin resistance occurs in different tissues including skeletal muscle, liver, and adipocytes.

In the prandial state, hepatic insulin resistance occurs by an impaired suppression of hepatic glucose production (HGP) by insulin. During the state of fasting hyperinsulinemia, basal
HGP is relatively decreased in isolated IFG subjects, indicating severe hepatic resistance to insulin.

During the post absorptive period, hepatic insulin resistance is manifested by a normal or slightly decreased rate of basal HGP in the presence of fasting hyperinsulinemia, and the product of fasting plasma insulin concentration and basal HGP reflects the severity of hepatic insulin resistance. Persons with IGT do have hepatic insulin resistance, but the intensity of insulin resistance is low when compared to persons with IFG (Abdul-Ghani MA, et al., 2006).

Insulin is a potent inhibitor of lipolysis. IGT subjects have an increased fasting plasma free fatty acid (FFA) concentration, suggesting an increased rate of lipolysis in adipocytes. Since the fasting plasma insulin concentration in subjects with IGT is elevated, an increased fasting plasma FFA concentration in the presence of fasting hyperinsulinemia indicates the presence of resistance to the antilipolytic action of insulin in adipocytes. Furthermore, the postprandial suppression of plasma FFA concentration (e.g. following a meal or an OGTT) is impaired in subjects with IGT despite marked hyperinsulinemia.

Because elevated plasma FFA concentrations cause insulin resistance in skeletal muscle and hepatocytes, an increase in the day-long concentration of plasma FFA in subjects with IGT is likely to contribute to their increased insulin resistance in skeletal muscle. Unlike IGT, individuals with isolated IFG have fasting plasma FFA concentration comparable to that of NGT subjects, suggesting a normal or near normal rate of lipolysis in IFG subjects. However, the normal rate of lipolysis in subjects with isolated IFG is achieved in the presence of fasting hyperinsulinemia. Thus, under conditions of normal fasting insulin concentration, subjects with isolated IFG would be expected to have an increased rate of lipolysis. Thus, IFG subjects (similar
to IGT individuals) have increased resistance to the antilipolytic effect of insulin (Muhammad A. Abdul-Ghani & Ralph A. DeFronzo, 2009).

In both IFG and IGT subject’s adipocytes insulin resistance is present. Subjects with IFG have severe hepatic insulin with near normal skeletal muscle insulin sensitivity. Subjects with IGT have a marked raise in skeletal muscle insulin resistance with only a mild elevation in hepatic insulin resistance.

The level of insulin resistance is a continuous process and its severity is directly linked to degree of glucose intolerance. When whole body insulin sensitivity is related to 2 hour plasma glucose concentration, it precipitously decreases with the increase in 2 hour plasma glucose concentration, the decrease in whole body insulin sensitivity starts at plasma glucose concentrations considered to be within the normal range.

The rise in insulin resistance in subjects with prediabetes is accompanied by a cluster of metabolic abnormalities (obesity, hypertension, and dyslipidemia), all of which are important risk factors for cardiovascular disease (De Fronzo, 1997; Reaven, 1988). This condition is clinically referred as insulin resistance (metabolic) syndrome.

The prevalence of metabolic syndrome is raised to 2-3 folds in the prediabetic subjects in comparison to normal subjects (Alexander CM et al., 2003). The increased prevalence of the metabolic syndrome in subjects with prediabetes is the major contributing factor to their increased cardiovascular risk despite the presence of normoglycemia (Cersosimo E & DeFronzo RA, 2006).

**Insulin Secretion in Prediabetes**

Although insulin resistance is maximally manifested early in the natural history of T2DM (i.e. subjects with IGT and NGT who are offspring of two T2DM parents), progressive \( \beta \)-cell
failure is the principle factor responsible for the development and progression of T2DM. Glucose stimulated insulin secretion is impaired in both IFG and IGT. Under physiological conditions, the major route of glucose ingestion is by the gastrointestinal tract, where it stimulates the secretion of the incretin hormones (glucagon-like peptide 1 [GLP-I] and gastric inhibitory peptide [GIP]) that act on the β cell to stimulate insulin secretion. In both IFG and IGT, insulin secretion rate demonstrated a marked impairment in β-cell function. However, the pattern of impairment in β-cell function is quite distinct in subjects with IGT and IFG. Although subjects with IGT have severe defect facts in both the early (0–30 minute) and late (60–120 minute) phases of insulin secretion, only early phase insulin secretion is impaired in IFG subjects who manifest a supranormal second-phase insulin secretion. The mechanism of β-cell failure is not clearly understood but a progressive reduction in β-cell sensitivity to glucose appears as the 2 hour plasma levels of glucose are elevated (Ferrannini E et al., 2005). The incretin hormones like GLP-I and GIP act on the β cell to potentiate glucose-stimulated insulin secretion. A decrease in the level of the incretin hormones (GLP-1) or resistance to incretin hormones (GIP) in subjects with prediabetes could contribute to the decrease in β-cell glucose sensitivity and impaired insulin secretion as 2 hour plasma glucose increases (Muhammad A. Abdul-Ghani & Ralph A. DeFronzo, 2009).

**Management for Prediabetes**

A diagnosis of prediabetes identifies an individual at high risk of developing T2DM and at increased risk of CVD. There are several reasons why treating prediabetes to prevent progression to overt T2DM might be beneficial (Glenn Martin & Richard E. Pratley, 2010). The treatment goal of prediabetes is to prevent future development of type 2 diabetes and diabetes related complications.
Lifestyle modifications

- Lifestyle modification should be the cornerstone of treatment for prediabetes; it should be attempted with all patients and reinforced in every visit with the health care professional.
- Lifestyle is a fundamental management approach that can effectively prevent or delay progression from prediabetes to diabetes, as well as reduce both microvascular and macrovascular disease risks.
- Importantly, lifestyle interventions improve the panoply of risk factors for diabetes and components of the metabolic syndrome: obesity, hypertension, dyslipidemia, and hyperglycemia.
- Persons with prediabetes should reduce weight by 5% to 10%, with long term maintenance at this level, on the basis of the Diabetes Prevention Program findings. Even this modest degree of weight loss results in decreased fat mass, blood pressure, glucose, low density lipoprotein cholesterol, and triglycerides. These benefits can also translate into improved long term outcome, especially if weight loss and lifestyle alterations are maintained.
- In long term follow up from the Finnish Diabetes Prevention Program lifestyle intervention in people at high risk for type 2 diabetes resulted in sustained lifestyle changes and reduction in diabetes incidence, which persisted after individual lifestyle counseling, was stopped (Lindström J et al., 2006).
- A program of regular moderate intensity physical activity for 30 to 60 minutes daily, at least 5 days weekly, is recommended. A diet that includes calorie restriction, increased fiber intake, and possible limitations in carbohydrate intake is advised (V. Mohan et al., 2007).

Exercise
In prediabetic subjects peripheral glucose uptake and insulin sensitivity are improved by translocation of insulin responsive glucose transporters (GLUT4) to the cell surface by regular exercise. Long term moderate exercise leads to more efficient energy use by increasing mitochondrial enzymes, the number of slow switch muscle fibres, and the generation of new capillaries (Henriksson J, 1992). The protective effects of physical activity had been studied in two prospective cohort studies where the development of type 2 diabetes was significantly lower in subjects who exercised regularly (Samy I. McFarlane et al., 2003).

**Weight loss**

High percentage of body fat, especially abdominal obesity is one of the modifiable risk factor for the development of diabetes (Bjorntorp P, 1988). Progression of IGT to diabetes and the impact of weight loss were observed in different studies. In a prospective randomized controlled study involving 154 over weight individuals with family history of diabetes (one or both parents), modest weight loss of 4.5 kg reduced the risk of type 2 diabetes by approximately 30% compared with no weight loss.

**Medical Weight-Loss Strategies**

Bariatric surgery is effective in decreasing the incidence of diabetes development in patients who are morbidly obese (body mass index greater than 40 kg/m$^2$) or who have other significant risk factors, but not for subjects with prediabetes.

**PHARMACOLOGICAL INTERVENTIONS**

**Biguanides (Metformin)**

Metformin reduced the progression of prediabetes to diabetes by 31%, compared with placebo, a risk reduction somewhat less than that seen in the lifestyle intervention group (58%). Furthermore, the number needed to treat with metformin to prevent one case of diabetes in 3
years was 13.9, compared with 6.9 in the lifestyle intervention group in the Diabetes Prevention Program trial (Knowler WC et al., 2002).

Metformin is a potent insulin sensitizing agent that acts primarily by suppressing hepatic glucose production. Metformin inhibits free fatty acid (FFA) production and oxidation, thereby reducing FFA induced insulin resistance and hepatic glucose production. Metformin also has favorable effects in patients with the metabolic syndrome, as demonstrated in the BIGPRO (Biguanides and Prevention of Risks in Obesity) study (Fontbonne A et al., 1996). It also improves lipid profiles with a reduction in total cholesterol, LDL cholesterol and triglycerides and raise in HDL. These are not implied with weight gain and causes modest weight loss therefore, they are good initial medications (Lenna Liu et al., 2004).

Thiazolidinediones

The thiazolidinedione, troglitazone, has been shown to prevent or delay the incidence of type 2 diabetes, compared with placebo, in a group of 133 high-risk Hispanic women with a history of gestational diabetes followed for 30 months. Troglitazone prevention of diabetes was proportional to the reduction in plasma insulin level after 3 months of treatment in the Troglitazone in the Prevention of Diabetes study (Buchanan TA et al., 2002). These results are consistent with the notion that thiazolidinediones prevent diabetes by ameliorating insulin resistance.

The mechanism of action of thiazolidinediones involves binding to the peroxisome proliferator activated receptor-γ, a transcription factor that regulates the expression of specific genes, especially in fat cells, but also in other tissues. It is likely that thiazolidinediones primarily act in adipose tissue, where peroxisome proliferator activated receptor-γ is predominantly expressed. Thiazolidinediones have been shown to interfere with the expression
and release of mediators of insulin resistance originating in adipose tissue (e.g., FFAs, adipocytokines, such as tumor necrosis factor α, resistin, adiponectin) in a way that results in net improvement of insulin sensitivity in muscle and liver (Stumvoll M and Haring HU, 2002).

**α-Glucosidase inhibitors**

In a multicenter, randomized, placebo-controlled Study to Prevent non insulin dependent diabetes mellitus trial 714 subjects were randomized to acarbose and 715 to placebo and were followed for 3 years to examine the ability of acarbose to prevent type 2 diabetes in subjects with IGT. Thirty two percent of subjects randomized to acarbose, and 42% of those randomized to placebo, developed diabetes, a relative risk reduction of 25%. Additionally, acarbose significantly increased reversion of IGT to normal glucose tolerance (Chiasson JL *et al.*, 2002). Acarbose improves both insulin secretion and sensitivity by reducing postprandial blood glucose.

**ACE inhibitors and Angiotensin Receptor Blockers**

The ACE inhibitor captopril decreased the progression of diabetes by 14%, compared with the β blocker or thiazide diuretic treatment arm in the Captopril Prevention Project randomized trial (Hansson I *et al.*, 1999). In the Heart Outcomes Prevention Evaluation study the possibility of an ACE inhibitor (ramipril) to prevent diabetes in which patients with high risk for CVD were randomized to receive either ramipril or placebo in 5720 individuals without prior history of diabetes followed for 4.5 years. Ramipril was shown to decrease the development of type 2 diabetes by 34% compared with placebo (Yusuf S *et al.*, 2000). Angiotensin receptor I blockers (ARBs) may also prevent diabetes. There was a 25% lower incidence of new onset diabetes in the losartan group, an ARB, when compared to the Atenolol group in the Losartan Intervention for Endpoint reduction in hypertension trial (Lindholm LH *et al.*, 2002).
The mechanism by which ACE inhibitors and ARB therapy reduce the progression of type 2 diabetes in patients at risk is not clear. However, there appears to be postreceptor insulin signaling abnormalities associated with insulin resistance. These signaling abnormalities are accentuated by angiotensin II, and include alterations in phosphatidylinositol 3-kinase (PI3-K) and protein kinase B (Akt) signaling abnormalities. Thus, interruption of the renin-angiotensin system may be one mechanism for improving insulin sensitivity, and thereby preventing or delaying the onset of diabetes.

**Statins**

The development of new diabetes was examined in men aged 45 to 64 years in the subanalysis of the West of Scotland Coronary Prevention Study; pravastatin therapy reduced the risk of developing diabetes by 30%. This prevention in the onset of diabetes was associated with significant reduction in triglyceride levels (Freeman DJ *et al.*, 2001). Statins may affect substrate delivery to insulin sensitive tissues or modulate insulin-activated signaling cascades that mediate glucose uptake. Statins also increase nitric oxide synthase expression, which may result in increased capillary recruitment and glucose disposal (McFarlane SI *et al.*, 2002). Insulin activates a series of kinase cascades that include PI3-K and Akt, resulting in the translocation of glucose transporters to cell membrane and enhanced glucose uptake. This cascade inhibited by circulating cytokines. Statins, like insulin, in addition to decreasing cytokine levels, also inhibit the cellular cascade, such as Rho-kinase, that inactivates the insulin receptor and signaling. These mechanisms might explain, in part, the reduction in the risk of developing diabetes observed with statins (Freeman DJ *et al.*, 2001). Additional use of fibrates, bile acid sequestrants, ezetimibe, and other agents should be considered as appropriate. Bile acid
sequestrants may play a unique role in prediabetes because one of the drugs in this class colesevelam reduces glucose levels (Morali D. Sharma et al., 2009).

**Anti-platelet Therapy**

Low dose aspirin is recommended for all persons with prediabetes for whom there is no identified excess risk for gastrointestinal, intracranial, or other hemorrhagic condition. In platelets a major cyclooxygenase product thromboxane A\(_2\), a labile inducer of platelet aggregation and a potent vasoconstrictor is present. Aspirin blocks thromboxane A\(_2\) by covalently acetylating serine residue near the active site of cyclooxygenase. Since the platelets do not synthesize any new proteins, the action of aspirin on platelet cyclooxygenase is permanent (7-10 days) (Goodman & Gilman’s, 2001).
Section – III

Biomarkers Evaluated in the Study
BIOMARKERS EVALUATED IN THE STUDY

Biomarker is a biological indicator of characteristic that is objectively measured and evaluated as an indicator of normal biological processes, pathological processes, or pharmacological responses to a therapeutic intervention.

They are used to monitor and predict the health of a population, to identify individuals with particular resistance or susceptibility to health problems, and to evaluate therapeutic interventions. Biomarkers are much better predictors of disease (illness) and death than self-reported health status (Noreen Goldman, 2007). Even when individuals have already provided information on their physical, mental, and cognitive health, biomarkers provide additional information about their health status. Biomarkers can provide reliable substitutes for clinical responses. In diabetes mellitus estimation of biomarkers is useful to assess glycemic control, insulin sensitivity, inflammation, microvascular complications, endothelial function and many other biological processes.

Fasting Glucose

Fasting is defined as no caloric intake for at least 8 hours. Fasting glucose level measures amount of sugar in blood in fasting state and it is the main indicator of diabetes mellitus. Normal blood glucose level was ≤ 7.0 mM or ≤ 110 mg/dL.

Lipid Profile

Dyslipidemia is defined as abnormal amounts of lipids in the blood. The abnormally high concentration of serum lipids in diabetes is mainly a result of the increase in mobilization of free fatty acids from peripheral depots, because insulin inhibits the hormone sensitive lipase. On other hand, glucagon, catecholamine, and
other hormones enhance lipolysis. The marked hyperlipidemia that characterizes the diabetic state may therefore be regarded as a consequence of the uninhibited actions of lipolytic hormones on fat depots. The increase and fall in the individual lipoprotein levels is a reflection of the total serum cholesterol; that is, the levels of VLDL, LDL, and HDL increase or decrease with the level of total serum cholesterol, and it is their ratio that determines the pathophysiology of lipoprotein metabolism (P. Pasupathi et al., 2009).

The main reason for mortality in type 2 diabetes is CVD. According to the Scandinavian Simvastatin Survival Study, the Cholesterol And Recurrent Events (CARE) study (Pteffer MA et al., 1995) and the helsinki heart study, dyslipidemia is an independent risk factor for CVD in people with diabetes.

Total cholesterol: This aids in the synthesis of bile acids and steroid hormones. Associated health outcomes with this marker in middle age are: CHD and all cause mortality and in older ages it shows U-shaped relation to death.

Low density lipoprotein (LDL): This transports cholesterol from the liver to be incorporated into cell membrane tissues. Associated health outcomes are CHD, atherosclerosis, stroke, peripheral vascular disease.

High density lipoprotein cholesterol (HDL): This is protective cholesterol and it lowers atherosclerotic CVD.

Triglycerides: This is a fat substance stored for energy use. Associated health outcomes with this marker are heart attack, CHD, coronary artery disease, pancreatitis.
Liver Enzymes

Serum Glutamic Oxaloacetic Transaminase (SGOT)

SGOT is present in all human tissues of the body. Significant amounts are present in liver, kidneys, heart and skeletal muscles. When any of these organs is damaged or diseased, serum GOT level rises. The rise is proportional to extent of damage. High prevalence of elevated liver enzymes in type 2 diabetes was reported by Forlani G et al., 2008.

Serum Glutamic Pyruvic Transaminase (SGPT)

High concentrations of SGPT are present in liver, kidneys, heart and skeletal muscle tissue. At lower concentrations it is also present in lungs, spleen, pancreas, brain and erythrocytes. Primary liver diseases (cirrhosis, carcinoma, viral or toxic hepatitis) as well as liver damage secondary to other causes result in elevated SGPT levels.

Gamma Glutamyl Transferase (GGT)

GGT is one of the most sensitive enzymes of the hepatobiliary system. Elevated serum gamma-GT level is surrogate marker of liver dysfunction and nonalcoholic fatty liver, are considered as part of metabolic syndrome and related type 2 diabetes.

Serum Urea

Urea is the major end product of protein metabolism in humans. It constitutes the largest fraction of the non-protein nitrogen component of the blood. Urea is produced in the liver and excreted through the kidney in urine. Consequently, the circulating levels of urea depend upon protein intake, protein catabolism and kidney function. Recent evidence from many clinical and
epidemiological researches suggests that serum uric acid level is an important marker of hypertension, coronary heart disease, renal disease, and diabetes (Nan H et al., 2007).

**Serum Creatinine**

It is a metabolic waste product formed in the muscle from the high energy storage compound, creatinine phosphate. The amount of creatinine produced is fairly constant and is primarily a function of muscle mass. It is removed from plasma by glomerular filtration and then excreted in urine without any appreciable reabsorption by the tubules. Creatinine is a useful indicator of renal function. Some recent studies have shown abnormal serum creatinine levels were associated with type 2 diabetes mellitus (B. Shivananda Nayak et al., 2011).

**Serum Electrolytes**

Electrolytes are essential for normal function of cells and organs. Sodium is the major positive ion in fluid outside of cells and potassium is the major positive ion found inside of cells.

Many researchers had reported abnormal electrolyte changes in diabetes (Syed Muhammad Shahid and Tabassum Mahaboob, 2008; Issautier et al., 1994). Serum electrolyte measurements are useful for screening electrolyte and acid-base imbalance along with assessing the effect of treatment on a known imbalance.

**Hematology (RBC, WBC & Hemoglobin)**

In recent years some researchers have shown increased anemia, increased RBC count and variation in WBC count in diabetes patients (D. Simmons, 2010; Jing – Yan Tian et al., 2008; Ishimura et al., 1998). Chronic subclinical inflammation has been recognized to play a central role in both initiation and progression of type 2 diabetes and cardiovascular diseases. Activation of the
inflammation may be detected by an increase in number of markers, including WBC count, C-reactive protein, interleukin-6, plasminogen activator inhibitor-1, etc (Martijn van Doorn et al., 2005). In the present study WBC count was estimated as an inflammatory marker.
Bibliography


