# Diabetes mellitus associated with Hypertension

A thesis project submitted to the department of pharmacy, East West University, Bangladesh, in partial fulfillment of the requirements for the degree of Bachelor of Pharmacy.


***Submitted by***

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***ID: 2007-1-70-060***




Submission Date: **January, 2012**

East West University

# CERTIFICATE

This is to certify that, the research paper, titled "diabetics mellitus associated with hypertension", is submitted to the Department of Pharmacy, East West University, Mohakhali, Dhaka for the partial fulfillment of the requirements for the degree of Bachelor of Pharmacy (B. Pharm.) and the research was carried out by Rasel Mahmud (ID# 2007-1-70-060) under our guidance and supervision and that no part of the thesis has been submitted for any other degree We further certify that the sources of information and laboratory facilities availed of this connection is duly acknowledged.

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# CERTIFICATE

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# Acknowledgements

First and foremost I would like to thank the Almighty Allah for proving me gift of life then; I would like thank my parents for their support, which helps me to complete my study.

I would like to express exclusive my thanks and sincere gratitude to my Supervisor, ***Kh.Tanvir Ahamed,*** Lecturer, Department of Pharmacy, East West University, Bangladesh, for her adroit supervision, benevolent guidance and relentless encouragement throughout the period of the research work and in completion of this dissertation.

Besides, I am grateful to my co-supervisor ***Mrs. Momena Shirin*** M.Phil (PSM), superintendent, I.V. fluid, Institute of Public Health, Mohakhali, Dhaka for her guidance, criticism and encouragement during the preparation of this study.

I would like to express my gratitude to the Chairman of Department of Pharmacy of East-West University, ***Dr. Sufia Islam***, for giving me all the necessary support and facilities to complete this research work.

I also thanks to my class mate and friend Rubaite Arjumand.

I am especially thankful to the entire patient and the stuff of the medical who were very helpful to me.

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# Abstract

Diabetes mellitus is the rapid development disease that caused by metabolic disorder. There are many several risk factors exists, among them, hypertension and smoking is the most important. To find out the relationship between hypertension with diabetes mellitus the present study was conducted incorporating 105 patients from the Bangladesh Institute of Research and Rehabilitation in Diabetes, Endocrine and Metabolic Disorders (BIRDEM). In this survey type study data were collected using a questionnaire which include question regarding name, address, sex, age, education, marital status, occupation, smoking, betel nut, table salt etc. All data were evaluated and compared with each patient. The results of the study showed that 70% patients were male and 30% patients werefemale. Among the patients 57% people were attacked by hypertension. The distribution of diabetes mellitus in different age range showed that from 40-59 years, people are more prone to suffering from diabetes mellitus. It was also found that 43% of total population was suffering from leg problem associated diseases. The results of the study suggested that diabetes mellitus is more prevalent in hypertensive patients, which ultimately results in a complication and increases morbidity and mortality.Diabetes mellitus is a common metabolic disorder where smoking and hypertension is giving synergistic effect on patients. Since smoking and hypertension is modifiable risk factor, a person can remain safe from this disease by changing their lifestyle. Physical activity and nutritious food are essential for every person. Moreover, smoking should be abandoned and blood pressure should be in control.

This thesis paper is dedicated to my parents

# Chapter one

# Introduction

## 1.0 Diabetes Mellitus

Diabetes mellitus is a group of metabolic diseases characterized by high blood sugar (glucose) levels that result from defects in insulin secretion, or action, or both. Diabetes mellitus, commonly referred to as diabetes was first identified as a disease associated with "sweet urine," and excessive muscle loss in the ancient world. Elevated levels of blood glucose (hyperglycemia) lead to spillage of glucose into the urine, hence the term sweet urine.

Normally,blood glucose levels are strictly controlled by insulin, a hormone produced by the pancreas. Insulin lowers the blood glucose level. When the blood glucose elevates from normal value (for example, after eating food), insulin is released from the pancreas to normalize the glucose level. In patients with diabetes, the absence or insufficient production of insulin causes hyperglycemia. Diabetes is a chronic medical condition, meaning that although it can be controlled, it lasts a lifetime.[1]

### 1.1 Cause of Diabetes Mellitus

The word "diabetes" is borrowed from the Greek word meaning "a siphon". Aretus the Cappadocian, a Greek physician during the second century A.D., named the condition diabainein. He described patients who were passing too much water (polyuria) like a siphon. The word became "diabetes" from the English adoption of the Medieval Latin diabetes.

In 1675 Thomas Willis added mellitus to the term, although it is commonly referred to simply as diabetes. Mel in Latin means honey; the urine and blood of people with diabetes has excess glucose, and glucose is sweet like honey. Diabetes mellitus could literally mean "siphoning off sweet water".

In ancient China people observed that ants would be attracted to some people's urine, because it was sweet. The term "Sweet Urine Disease" was coined.[2]

## 1.2 Classification of Diabetes Mellitus

### 1.2.1 Type 1 Diabetes

Type 1 Diabetes mellitus is characterized by loss of the insulin-producing beta cells of the islets of Langerhans in the pancreas leading to insulin deficiency. This type of diabetes can be further classified as immune-mediated or idiopathic. The majority of type 1 diabetes is of the immune-mediated nature, where beta cell loss is a T-cell mediatedautoimmune attack.[3] There is no known preventive measure against type 1 diabetes, which causes approximately 10% of diabetes mellitus cases in North America and Europe. Most affected people are otherwise healthy and of a healthy weight when onset occurs. Sensitivity and responsiveness to insulin are usually normal, especially in the early stages. Type 1 diabetes can affect children or adults but was traditionally termed "juvenile diabetes" because it represents a majority of the diabetes cases in children.

Brittle diabetes, also known as unstable diabetes or labile diabetes, refers to a type of insulin-dependent diabetescharacterized by dramatic and recurrent swings in glucose levels, often occurring for no apparent reason.[4] The result can be irregular and unpredictable hyperglycemias, frequently withketosis, and sometimes serious hypoglycemia. Brittle diabetes occurs no more frequently than in 1% to 2% of diabetics.[5]

### 1.2.2 Type 2 Diabetes

Type 2 Diabetes mellitus is characterized by insulin resistance which may be combined with relatively reduced insulin secretion. The defective responsiveness of body tissues to insulin is believed to involve theinsulin receptor. However, the specific defects are not known. Diabetes mellitus due to a known defect are classified separately. Type 2 diabetes is the most common type.

In the early stage of type 2 Diabetes, the predominant abnormality is reduced insulin sensitivity. At this stage hyperglycemia can be reversed by a variety of measures andmedications that improve insulin sensitivity or reduce glucose production by the liver.[6]

### 1.2.3 Gestational Diabetes

Gestational Diabetesis a temporary condition that occurs during pregnancy. This form of diabetes occurs more frequently among

- African Americans,
- Hispanic/Latino Americans, and
- Native Americans.

It is also common among obese women and women with a family history of diabetes.

## 1.3 Pathology of Diabetes Mellitus

### 1.3.1 Causes of Type 1 Diabetes

The pancreas can no longer make insulin and so the glucose cannot enter the muscle and other body cells, resulting in a rapid buildup of glucose and ketones in the blood stream. The kidneys attempt to wash this excess glucose out of the body so there is an increase in urine production, and the person becomes very thirsty. If glucose cannot be used by the cells, the bodies break down fat as an alternative energy source. By products of fat breakdown are the chemicals called ketones. If too many ketones accumulate in the blood stream they can cause serious illness, and is a medical emergency. The onset of Type 1 diabetes may be quite sudden and often the person has rapid and unplanned weight loss over several weeks. In adults it may appear more slowly.[7]

### 1.3.2 Causes of Type 2 Diabetes

Initially insulin is still produced by the pancreas, but is less effective than normal. This is called insulin resistanceand is an inherited characteristic made worse by carrying extra body fat. Because insulin is necessary for glucose to move from the blood stream into the body cells and the liver, excess glucose remains in the blood stream resulting in higher than normal blood glucose levels (BGLs). After several years of diabetes, the pancreas may become "exhausted" and produce less insulin.[7]

### 1.4 Treatment of Diabetes Mellitus

#### 1.4.1Type 1 Diabetes

Replacement of insulin via injections (usually several times a day), balanced with healthy eating and guided by regular monitoring of blood glucose levels.

Regular visits to the doctor and other health care professionals (diabetes nurse educator, dietitian and podiatrist.) [7]

#### 1.4.2 Type 2 Diabetes

The aim of treatment is to control blood glucose levels and to prevent long term problems associated with diabetes such as heart disease.

Healthy eating and physical activity are the first steps to getting blood glucose levels and blood pressure under control. If blood glucose levels are not well enough controlled with diet and exercise, anti-diabetic tablets may be necessary. Many people with Type 2 diabetes will also require insulin injections at some stage to manage their diabetes.[7]

### 1.5 Symptoms:

Signs and symptoms of diabetes include the following:

- Unusual thirst
- Frequent urination
- Weight change (gain or loss)
- Extreme fatigue or lack of energy
- Blurred vision
- Frequent or recurring infections
- Cuts and bruises that are slow to heal
- Tingling or numbness in the hands or feet

Note: Many people who have Type 2 diabetes may display no symptoms.[8]

### 1.6 Pre-Diabetes

This condition raises the risk of developing Type 2 diabetes, heart disease, and stroke. People with pre-diabetes have blood glucose levels higher than normal but not at the level of diabetes. Progression to diabetes is not inevitable; people can prevent or delay onset and work to decrease their blood glucose levels if they lose weight and increase their physical activity. [8]

### 1.7 Complications:

If left untreated or improperly managed, diabetes can result in a variety of complications such as:

- Heart disease
- Kidney disease
- Eye disease
- Impotence
- Nerve damage [8]

### 1.8 Risk factors:

- Being a member of a high risk group (Latino/Hispanic American, African American, Asian American, Native American)
- Being overweight (especially if you carry most of your weight around the middle)
- Having family history of diabetes
- Have health complications that are associated with diabetes
- High blood pressure
- High cholesterol or other fats in the blood [8]

### 1.9 History

Diabetes is one of the oldest known diseases. [9] An Egyptian manuscript from c. 1550 BCE mentions the phrase "the passing of too much urine."[9] The great Indian physician

Sushruta(fl. 6th century BCE) [9] identified the disease and classified it as Medhumeha.[10] He further identified it with obesity and sedentary lifestyle, advising exercises to help "cure" it.[10] The ancient Indians tested for diabetes by observing whether ants were attracted to a person's urine, and called the ailment "sweet urine disease" (Madhumeha).

Concerning the sweetness of urine, it is to be noted that the Chinese, Japanese and Korean words for diabetes are based on the same ideographs which mean "sugar urine disease". It was in 1776 that Matthew Dobson confirmed that the sweet taste comes from an excess of a kind of sugar in the urine and blood.[11]

The first complete clinical description of diabetes was given by the Ancient GreekphysicianAretaeus of Cappadocia (fl. 1st century CE), who noted the excessive amount of urine which passed through the kidneys and gave the disease the name "diabetes."[9]

Diabetes mellitus appears to have been a death sentence in the ancient era. Hippocrates makes no mention of it, which may indicate that he felt the disease was incurable. Aretaeus did attempt to treat it but could not give a good prognosis; he commented that "life (with diabetes) is short, disgusting and painful."[12]

In medieval Persia, Avicenna (980–1037) provided a detailed account on diabetes mellitus in The Canon of Medicine, "describing the abnormal appetite and the collapse of sexual functions," and he documented the sweet taste of diabetic urine. Like Aretaeus before him, Avicenna recognized primary and secondary diabetes. He also described diabetic gangrene, and treated diabetes using a mixture of lupine, trigonella (fenugreek), and zedoary seed, which produces a considerable reduction in the excretion of sugar, a treatment which is still prescribed in modern times. Avicenna also "described diabetes insipidus very precisely for the first time", though it was later Johann Peter Frank (1745–1821) who first differentiated between diabetes mellitus and diabetes insipidus.[13]

Although diabetes has been recognized since antiquity, and treatments of various efficacy have been known in various regions since the Middle Ages, and inlegend for much longer, pathogenesis of diabetes has only been understood experimentally since about 1900.[14] The discovery of a role for the pancreas in diabetes is generally ascribed toJoseph von Meringand

Oskar Minkowski, who in 1889 found that dogs whose pancreas was removed developed all the signs and symptoms of diabetes and died shortly afterwards.[15] In 1910, Sir Edward Albert Sharpey Schafer suggested that people with diabetes were deficient in a single chemical that was normally produced by the pancrea she proposed calling this substance *insulin*, from the Latin *insula*, meaning island, in reference to the insulin-producingislets of Langerhans in the pancreas.

The endocrine role of the pancreas in metabolism, and indeed the existence of insulin, was not further clarified until 1921, when Sir Frederick Grant Banting and Charles Herbert Best repeated the work of Von Mering and Minkowski, and went further to demonstrate they could reverse induced diabetes in dogs by giving them an extract from the pancreatic islets of Langerhans of healthy dogs.[16] Banting, Best, and colleagues (especially the chemist Collip) went on to purify the hormone insulin from bovine pancreases at the University of Toronto. This led to the availability of an effective treatment insulin injections and the first patient was treated in 1922. For this, Banting and laboratory director MacLeod received the Nobel Prize in Physiology or Medicine in 1923; both shared their Prize money with others in the team who were not recognized, in particular best and Collip. Banting and Best made the patent available without charge and did not attempt to control commercial production. Insulin production and therapy rapidly spread around the world, largely as a result of this decision. Banting is honored by World Diabetes Day which is held on his birthday, November 14.

The distinction between what is now known as type 1 diabetes and type 2 diabetes was first clearly made by Sir Harold Percival (Harry) Himsworth, and published in January 1936.[17]

Despite the availability of treatment, diabetes has remained a major cause of death. For instance, statistics reveal that the cause-specific mortality rate during 1927 amounted to about 47.7 per 100,000 populations in Malta.

## 1.10 Discovery of Diabetes

**In fifteen hundred fifty two BCE-**

Egyptian physician Hesy-Ra of the 3rd Dynasty makes the first known mention of Diabetes found on the Ebers Papyrus and lists remedies to combat the passing of too Much urine.

**In two hundred fifty BCE-**

Diabetes described by Arateus as 'the melting down of flesh and limbs into urine.

**In one hundred twenty CE-**

Greek physician Aretaeus of Cappodocia gives the first complete medical description of diabetes, which he likens to 'the melting down of flesh and limbs into urine.

**In fourteen hundred twenty five-**

Diabetes first appears in the English language as the Middle English word 'diabetes'.

**In sixteen Century-**

Swiss physician PhillipusAureolus Paracelsus considered the 'Martin Luther of Medicine' identifies diabetes as a serious general disorder.

**In sixteen hundred seventy four-**

In his treatise Pharmaceutics rationales, Professor Thomas Willis of Oxford University describes the 'wonderfully sweet' flavor of urine in diabetes mellitus.

**In seven hundred seventy six-**

English physician Matthew Dobson of Liverpool evaporates two quarts of urine from a patient with diabetes. The resulting residue is granulated and smells and tastes like sugar, conclusively establishing the presence of 'saccharine materials' as a diagnosis of diabetes.

**In seven hundred ninety seven-**

Scottish physician John Rollo creates the first medical therapy to treat diabetes. He prescribes an 'animal diet' for his patients of 'plain blood puddings' and 'fat and rancid meat' so to manage the disease with foods their bodies could assimilate.

**In eighteen hundred sixty nine-**

German medical student Paul Langerhans discovers the islet cells of the pancreas but is unable to explain their function. The find is dubbed the 'islets of Langerhans.

**In eighteen hundred seventy one-**

French physician Apollinaire Bouchardat notices the disappearance of glycosuria in his diabetes patients during food rationing of food under the Siege of Paris in the Franco-Prussian War, and formulates individualized diets to treat the condition.

**In eighteen hundred eighty nine-**

Scientists Oskar Minkowski and Joseph von Mering of the University of Strasbourg, France demonstrate how removing a dog's pancreas produces diabetes.

**In eighteen hundred ninety one fourteen November-**

Frederick Banting is born on his parents' farm near Alliston, Ontario, north of Toronto.

**In eighteen hundred ninety nine twenty February-**

Charles Best born in West Pembroke, Maine.

**In nineteen hundred one-**

American pathologist Eugene Opie of John Hopkins University in Baltimore establishes a connection between the failure of the islets of Langerhans in the pancreas and the occurrence of diabetes.

**In nineteen hundred thirteen-**

Prof. John J.R. Macleod writes a monograph on diabetes entitled 'Diabetes: Its Pathological Physiology.

**In nineteen hundred sixteen December-**

Boston pathologist Elliott Joslin compiles 1,000 of his own cases and creates the textbook The Treatment of Diabetes Mellitus. In it he reports that 'the mortality of patients was approximately 20 per cent lower than for the previous year', due to 'the introduction of fasting and the emphasis on regular exercise.' This book and Joslin's subsequent research over the next five decades establishes his reputation as one of the world's leading expert in diabetes.

**In nineteen hundred nineteen-**

Dr. Frederick Allen of the Rockefeller Institute in New York publishes his Total Dietary Regulations in the Treatment of Diabetes that introduces a therapy of strict dieting dubbed the 'starvation treatment' as a way to manage diabetes

**In nineteen hundred twenty first July-**

Banting opens his first medical practice in London, Ontario.

**In nineteen hundred twenty thirty one October-**

Banting conceives of the idea of insulin after reading an article in the journal Surgery, Gynecology and Obstetrics by Moses Barron, an American pathologist, titled 'The Relation of Islets of Langerhans to Diabetes with Special Reference to Cases of Pancreatic Lithiasis.' He moves to Toronto and over the next year, with the support of Prof.. Macleod of the University of Toronto, and the assistance of Best, a medical student, and Dr. James Collip, continues his research using a variety of different extracts on depancreatized dogs.

**In nineteen hundred twenty one summer-**

Banting's work leads to the discovery of insulin. On July 30, Dog 410 is the first to receive the extract. On August 4 the extract is called 'Isletin' for the first time.

**In nineteen hundred twenty one fourteen November-**

Dr. Banting and Charles Best deliver a preliminary report of their research to the Journal Club of the University of Toronto, Department of Physiology.

**In nineteen hundred twenty one seventeen November-**

Banting and Best discover that extract from cattle foetal pancreas lowers blood sugar levels of depancreatized dogs, leading them toward plentiful, cheap sources for insulin. Experiments begin to test the long-term effectiveness of insulin treatment.

**In nineteen hundred twenty one December-**

Dr. James Bertram Collip, a biochemist on sabbatical from the University of Alberta, joins the Banting and Best team to assist in refining the quality of extracts.

**In nineteen hundred twenty thirty December-**

Banting, Macleod, Best and Collip present the results of their research at a session of the American Physiological Society at Yale University. The paper initially generates little interest. The paper – 'The Internal Secretion of the Pancreas' – is published two months later in the prestigious Journal of Laboratory and Clinical Medicine.

**In nineteen hundred twenty two January-**

Leonard Thompson, 14, a 'charity patient' at the Toronto General Hospital, becomes the first person to receive and injection of insulin to treat diabetes. Thompson lives another 13 years before dying of pneumonia at age 27.

**In nineteen hundred twenty two May three-**

The word 'insulin' is used in public for the first time when Macleod presents the paper 'The Effect Produced on Diabetes by the Extracts of Pancreas' to the Association of American Physicians annual is meeting in Washington, D.C. The results of the Toronto group's experiments is hailed as 'one of the greatest achievements of modern medicine'.

**In nineteen hundred twenty two May thirty-**

Pharmaceutical manufacturer Eli Lilly & Co. of Indianapolis and the University of Toronto enter a deal for the mass production of insulin.

**In nineteen hundred twenty two August sixteen-**

Elizabeth Evans Hughes, 13, daughter of U.S. Secretary of State Charles Evans Hughes, arrives in Toronto to be treated by Banting for her diabetes. Weighing only 45 pounds and barely able to walk, Elizabeth responds immediately to the insulin treatment, and goes on to live a productive life. She dies in 1981 at age 73.

**In nineteen hundred twenty three October twenty five-**

Banting and Macleod are awarded the Nobel Prize in Physiology or Medicine. Banting shares his award with Best, while Macleod shares his with Collip.

**In nineteen hundred twenty three October-**

Insulin is made commercially available in the United States and Canada.

**In nineteen hundred thirty six-**

In a series of research papers, Sir Harold Himsworth of the University College Hospital in London finds that diabetes falls into two types based on 'insulin insensitivity.' This discovery later leads to the diabetes classifications of type 1 and type 2.

**In nineteen hundred thirty six-**

Hans Christian Hagedorn, founder of Novo Nordisk, discovers that adding protamine to insulin prolongs the duration of action of the medication.

**In nineteen hundred forty one February twenty one-**

At the height of the Second World War, Major Banting is killed in an airplane crash over Newfoundland while on a secret mission to England.

**In nineteen hundred forty four-**

The standard insulin syringe is introduced so to make diabetes management more uniform.

**In nineteen hundred forty nine-**

Best co-founds the Diabetic Association of Ontario.

**In nineteen hundred fifty three-**

Canadian Diabetes Association is established and Camp Banting, Canada's first camp for children with diabetes opens near Ottawa.

**In nineteen hundred fifty nine-**

Researchers identify type 1 diabetes (insulin dependent) and type 2 diabetes (non-insulin dependent).

**In nineteen hundred sixty six-**

First pancreas transplant performed at the University of Manitoba

**In nineteen hundred seventy one September fourteen-**

Anton Hubert Clemens receives the first patent for a portable blood glucose meter called the Ames Reflectance Meter. Dr. Richard K. Bernstein, an insulin dependent physician with diabetes, uses the meter to monitor his blood glucose at home, and subsequently publishes a report on his experiences.

**In nineteen hundred seventy-**

A group of interested physicians form the Clinical and Scientific Section (C&SS) of the Canadian Diabetes Association

**In nineteen hundred seventy two-**

The Canadian Diabetes Association establishes the Diabetes Educators Section (DES) to represent nurses, dietitians, physicians, social workers and other healthcare professionals.

**In nineteen hundred eighty two-**

Using recombinant DNA technology, pharmaceutical firm Eli Lilly develops the first biosynthetic human insulin – Humulinthat is identical in chemical structure to human insulin and can be mass produced.

**In nineteen hundred eighty nine July seven-**

Her Majesty Queen Elizabeth the Queen Mother kindles the Flame of Hope at Banting House National Historic Site – 'The Birthplace of Insulin' – in London, Ontario. As a symbol of hope, the flame will burn until a cure for diabetes is found.

**In nineteen hundred ninety one November five-**

As part of the 100th anniversary of Dr. Banting's birth, a time capsule created by the International Diabetes Federation Youth Representatives is entombed by Governor General Ray Hnatyshyn at Banting House in London, Ontario. The capsule will be opened when a cure for diabetes is found.

**In nineteen hundred ninety two-**

The Canadian Diabetes Association's Clinical Practice Guidelines published in the Canadian Medical Journal.

**In nineteen hundred ninety three-**

After 10 years of clinical study, the Diabetes Control and Complications Trial (DCCT) report is published and clearly demonstrates that intensive therapy delays the onset and progression of long-term complications in individuals with type 1 diabetes.

**In nineteen hundred ninety five-**

Canadian Diabetes Association launches its website which quickly becomes a source of diabetes-related information for people all over the world.

**In nineteen hundred ninety six-**

75th Anniversary of the discovery of insulin is celebrated around the world.

**In nineteen hundred eight-**

The United Kingdom Prospective Diabetes Study (UKPDS) scientifically inks the control of glucose levels and blood pressure control to the delay and possible prevention of type 2 diabetes.

**In nineteen hundred ninety eight-**

The Clinical Practice Guidelines for the Management of Diabetes in Canada is released by the Canadian Diabetes Association, and become a model for other nations health programs.

**In nineteen hundred ninety nine March-**

Scientists conduct the first successful islet transplant at the University of Alberta Hospital. The surgical procedure becomes known as The Edmonton Protocol.

**In nineteen hundred ninety nine July seven-**

Banting House is officially declared a National Historic Site. In a designation ceremony at Dr. Banting's historic home, Governor General Romeo LeBlanc unveils the Historic Sites and Monuments Board of Canada plaque.

**In two thousand three December fifteen-**

Canadian Diabetes Association posts the 2003 Clinical Practice Guidelines on its website as the first searchable, download-capable medical guidelines available online.

**In two thousand six December twenty-**

The United Nations recognizes diabetes as a global threat and designates World Diabetes Day, November 14 in honor of FrederickBanting's birthday as a UN Day to be observed every year starting in 2007.[18]

### 1.11 Magnitude of Diabetes Mellitus

Globally, non-communicable diseases (NCDs) are increasingly recognized as a major cause of morbidity and mortality. Diabetics have become a global disease. To create awareness on diabetics, 14 November is celebrated as World Diabetes Day jointly introduced lay WHO and internationally Diabetes Federation (IDF) in 2006.

#### 1.11.1 Diabetes World Wide

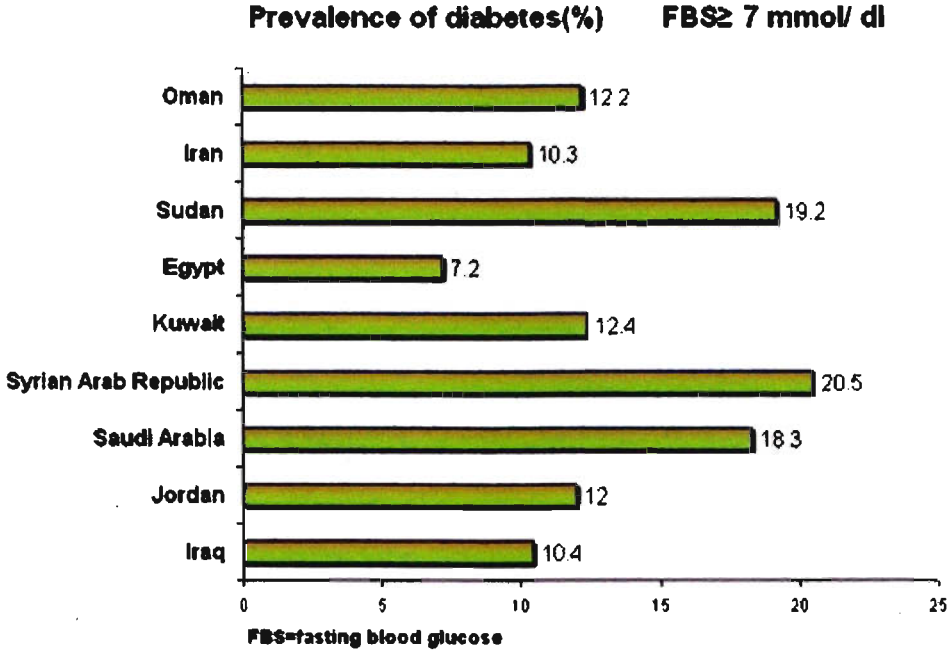
Diabetes has correctly been labeled as the "silent epidemic" its non dramatic, insidious and chronic nature often masks the menace inflicted by the disease through death, incapacitation, and negative impact on quality of life of patients as they spend years coping with their life changing affliction.

The World Health Organization is one of several organizations that monitor the worldwide patterns in diabetes. Some of the salient points extracted from recent reports on the state of diabetes clearly highlight the life threatening nature o the disease and its alarming rise in frequency:

- Worldwide 3.2 million diabetes-related deaths are reported annually, a number equivalent to that of HIV/AIDS-related deaths.
- One in every 20 deaths is attributed to diabetes equating to 8,700 deaths per day, or 6 deaths every minute.
- In the age group of 35-64 years, 1 out of 10 deaths are attributed to diabetes, a ratio that increases to 1 out of 4 in certain vulnerable populations.
- Diabetes contributes significantly to premature adult mortality – out of all deaths of diabetic people under the age of 35, three-fourths are attributable directly to the disease.
- Based on 2005 figures, at least 171 million people worldwide have diabetes. This number is expected to double by the year 2030.
- The condition is worse in developing countries, where the number of people afflicted by the disease are expected to increase by 150% by the year 2030.[19]

### 1.11.2 Diabetes in the Eastern Mediterranean Region

Prevalence of diabetes in some countries of the Eastern Mediterranean Region based on STEP wise surveillance.[20]



### 1.11.3 United States

The CDC reports that diabetes affects an estimated 21 million people in the U.S., and more than six million of these people are unaware they have the disease. According to the National Institute of Diabetes and Digestive and Kidney Diseases (NIDDK) and the American Diabetes Association, those affected include:

- 9.3 million U.S. women (8.7 percent of all women)
- 8.7 million U.S. men (8.7 percent of all men)
- 206,000 people under age 20
- 8.6 million Adults over age 60
- 2.7 million African Americans (11.4 percent of all African Americans)
- 2 million Hispanic/Latino Americans (8.2 percent of all Hispanic/Latino Americans)
- 12.5 million Caucasian Americans (8.2 percent of all Caucasian Americans)

Diabetes is the 6th leading cause of death and the 5th leading cause of death from disease. Diabetes costs the US $92 billion per year in direct medical costs and another $40 billion per year in indirect costs, such as loss of work, disability and loss of life.

The International Diabetes Federation estimates that there are 246 million adults with diabetes. The Western Pacific region and Europe have the highest number of people with diabetes, approximately 67 and 53 million, respectively. The highest prevalence rates are found in North America (9.2 percent) and Europe (8.4 percent). The five countries will the largest numbers of people with diabetes are India, China, the United States, Russia and Germany. The five countries with the highest prevalence rates are Nauru, United Arab Emirates, Saudi Arabia, Bahrain and Kuwait. The number of people with diabetes is expected to increase alarmingly in the coming decades, rising to 380 million peoples in 2025. Developed countries have higher prevalence rates than developing countries, but the latter will be hit the hardest by the diabetes epidemic. Increased urbanization, westernization and economic development in developing countries have already contributed to a substantial rise in diabetes.[21]

### 1.11.4 In Asia

The United Nations estimates the number of people globally affected by diabetes to be 246 million... and approximately half of those are in India, China, Nepal and other Asian countries.

Globally, Diabetes is ranked as the fourth leading cause of death, in terms of disease. Each year, an estimated 3.8 million people die from diabetes-related causes, such as:

- cardiovascular disease (heart disease),
- stroke (atherosclerosis),
- diabetic nephropathy (kidney disease),
- diabetic neuropathy (nerve disease),
- diabetic eye disease (retinopathy and macular oedema),
- Among many others.

The Nepal Diabetes Association (NDA) reports that among people aged 20 years and older living in urban areas, 15% are affected by this disease. Among people aged 40 years and older in urban areas, this number climbed to 19%.

One of the major causes of diabetes cited among the urban people was lack of needed physical activity.

However, the NDA also discovered that diabetes is a far less serious health problem in rural areas, where only 2% of the people aged 20 years and older were reportedly affected by diabetes.[22]

### 1.11.5 Sharp Rise in Asian Diabetes Rates

Research published in the medical journal *Lancet* reveals that life-threatening diabetes is becoming an epidemic not only in North America, but in Asia as well. And it appears to be only getting worse.

According to doctors at the Catholic University of Korea in Seoul, 194 million Asians were diabetic in 2003, a statistic that could soar to 330 million by the year 2025.

The Lancetresearch suggests Asians are developing diabetes at a younger age and at lower weight; they suffer longer with complications; and the also die earlier than people in developed countries. This onset of adult diabetes in increasingly younger populations will negatively affect Asian countries economically, as a result of higher health costs and mortality rates.

And while nearly one million people die from diabetes-related heart disease and stroke each year worldwide, another study in the *Lancet* also reveals that pre-diabetic conditions can be equally deadly. A Harvard School of Public Health team has found that elevated blood sugar below the diabetes threshold kills more than two times as many people every year as diabetes does specifically, 2.2 million people, with 84% of these living in developing countries.

"Of these 2.2 million, many of them are not called diabetics," says researcher MajidEzzati, who led the Harvard study. "They are people who could have benefited from lowering their blood glucose, but they are not at the threshold that we call disease."

When the total annual deaths from high blood sugar, including diabetes, are tallied together, the sum is over three million. Ezzati puts this number into perspective, by comparing it to the nearly five million deaths each year related to smoking, and the four million due to high blood cholesterol.[22]

### 1.11.6 Some More Asian Diabetes Statistic

According to the IDF's 2003 statistics, the top 5 countries with the largest number of diabetics were:

1. India – 35.5 million
2. China – 23.8 million
3. USA – 16.0 million
4. Russia – 9.7 million
5. Japan – 6.7 million [22]

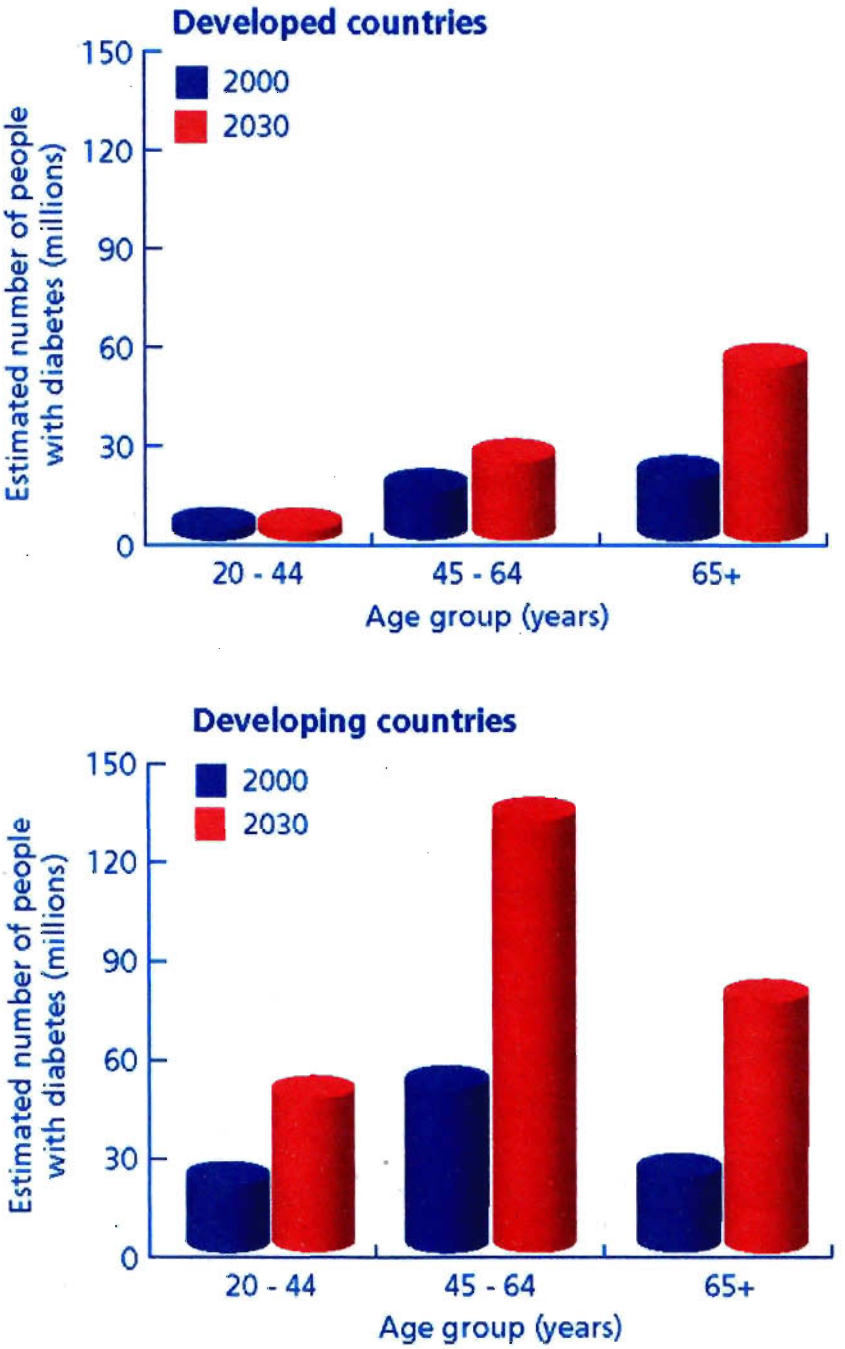
### 1.11.7 Diabetes in Developing Countries

The map shown is Figure 1.1 obtained from the WHO, shows the areas of the world that are worst affected by diabetes. As can be seen clearly in this map, diabetes afflicts two separate sections of the world:

Firstly, in the developed world, while diabetes has become a more mainstream disease, a large proportion of the patients are near or past the age of retirement. In the next section, facts and figures also show an increase of incidence in younger adults, largely as a function of lifestyle related parameters. But these changes are not as marked as they are in developing countries.

The map clearly illustrates South and South East Asia, the Middle East and parts of Northern Africa as the worst affected regions in the developing world. Both India and China have the largest number of diabetes patients, partly owing to their large populations. It is also well known that, in the developing world, the reported number of deaths related to diabetes is grossly underestimated poor surveillance and improper management of death records militates against clearly understanding the full impact of the disease.

What separates diabetes in the developing world from that in the developed world is its rapidly increasing incidence of the disease in the younger age group of 20-44 and 45-64 years. The graphs in Figure 1.2, obtained from the World Health Organization, illustrate the incidence of diabetes for different age brackets in both developed and developing nations, as well as its projected growth in the year 2030.[19]




Estimated number of adults with diabetes.

### 1.11.8 In Bangladesh

Higher prevalence of glucose intolerance and hypertension were also shown in a number of small epidermiological studies in Bangladesh. Diabetic insulin resistance, hypertension, and other coronary risk factors are more prevalent in Bangladesh.

In rural Bangladesh, prevalence of diabetes increased from 2.3% to 6.8% between 1999 and 2004.[23]

## 1.12 Hypertension

Hypertension is one of the most common worldwide diseases afflicting humans. Because of the associated morbidity and mortality and the cost to society, hypertension is an important public health challenge. Over the past several decades, extensive research, widespread patient education, and a concerted effort on the part of health care professionals have led to decreased mortality and morbidity rates from the multiple organ damage arising from years of untreated hypertension.

Approximately 50 million people in the United States are affected by hypertension. [24 25] Substantial improvements have been made with regard to improving awareness and treatment of hypertension. However, approximately 30% of adults are still unaware of their hypertension; up to 40% of people with hypertension are not receiving treatment; and, of those treated, up to 67% do not have their blood pressure (BP) controlled to less than 140/90 mm Hg. [25]

Hypertension is the most important modifiable risk factor for coronary heart disease (the leading cause of death in North America), stroke (the third leading cause), congestive heart failure, end-stage renal disease, and peripheral vascular disease. Therefore, health care professionals must not only identify and treat patients with hypertension but also promote a healthy lifestyle and preventive strategies to decrease the prevalence of hypertension in the general population.

### 1.13 Definition

Defining abnormally high blood pressure is extremely difficult and arbitrary. Furthermore, the relationship between systemic arterial pressure and morbidity appears to be quantitative rather than qualitative. A level for high BP must be agreed upon in clinical practice for screening patients with hypertension and for instituting diagnostic evaluation and initiating therapy. Because the risk to an individual patient may correlate with the severity of hypertension, a classification system is essential for making decisions about aggressiveness of treatment or therapeutic interventions.

### 1.14 Classification of hypertension

Based on recommendations of the Seventh Report of the Joint National Committee of Prevention, Detection, Evaluation, and Treatment of High Blood Pressure (JNC VII), the classification of BP (expressed in mm Hg) for adults aged 18 years or older is as follows:[25]

- Normal - Systolic lower than 120, diastolic lower than 80
- Prehypertension - Systolic 120-139, diastolic 80-90
- Stage 1 - Systolic 140-159, diastolic 90-99
- Stage 2 - Systolic equal to or more than 160, diastolic equal to or more than 100

The classification above is based on the average of 2 or more readings taken at each of 2 or more visits after initial screening. Normal BP with respect to cardiovascular risk is less than 120/80 mm Hg. However, unusually low readings should be evaluated for clinical significance.

Prehypertension, a new category designated in the JNC VII report, emphasizes that patients with prehypertension are at risk for progression to hypertension and that lifestyle modifications are important preventive strategies.

From another perspective, hypertension may be categorized as either essential or secondary. Essential hypertension is diagnosed in the absence of an identifiable secondary cause. Approximately 95% of the 50 million American adults with hypertension have essential

hypertension, while secondary hypertension accounts for fewer than 5% of the cases. However, secondary forms of hypertension, such as primary hyperaldosteronism, account for 20% of resistant hypertension (hypertension that requires 4 or more medications to control).

Especially severe cases of hypertension may be further categorized. Severe hypertension is defined by a blood pressure above 180/110 without symptoms. Hypertensive urgency is defined as a BP above 180/110 with mild end organ effects, such as headache and dyspnea. Hypertensive emergency is a BP of 220/140 or greater with life-threatening end-organ dysfunction.

Hypertensive emergencies encompass a spectrum of clinical presentations in which uncontrolled BPs lead to progressive or impending end-organ dysfunction; in these conditions, the BP should be lowered aggressively over minutes to hours. Acute end-organ damage in the setting of a hypertensive emergency may include the following:[26]

- Neurologic - Hypertensive encephalopathy, cerebral vascular accident/cerebral infarction. subarachnoid hemorrhage, intracranial hemorrhage
- Cardiovascular - Myocardial ischemia/infarction, acute left ventricular dysfunction, acute pulmonary edema, aortic dissection
- Other - Acute renal failure/insufficiency, retinopathy, eclampsia, microangiopathic hemolytic anemia

With the advent of antihypertensive, the incidence of hypertensive emergencies has declined from 7% to approximately 1%.[27] In addition, the 1-year survival rate associated with this condition has increased from only 20% (prior to 1950) to a survival rate of more than 90% with appropriate medical treatment.[27]

**1.15 Pathphysiology**

The pathogenesis of essential hypertension is multifactorial and highly complex. Multiple factors modulate the blood pressure (BP) for adequate tissue perfusion and include humoral mediators, vascular reactivity, circulating blood volume, vascular caliber, blood viscosity, cardiac output, blood vessel elasticity, and neural stimulation. A possible pathogenesis of

essential hypertension has been proposed in which multiple factors, including genetic predisposition, excess dietary salt intake, and adrenergic tone, may interact to produce hypertension. Although genetics appears to contribute to essential hypertension, the exact mechanism has not been established.

The natural history of essential hypertension evolves from occasional to established hypertension. After a long invariable asymptomatic period, persistent hypertension develops into complicated hypertension, in which target organ damage to the aorta and small arteries, heart, kidneys, retina, and central nervous system is evident. The progression begins with prehypertension in persons aged 10-30 years (by increased cardiac output) to early hypertension in persons aged 20-40 years (in which increased peripheral resistance is prominent) to established hypertension in persons aged 30-50 years, and, finally, to complicated hypertension in persons aged 40-60 years.

One mechanism of hypertension has been described as high-output hypertension. High-output hypertension results from decreased peripheral vascular resistance and concomitant cardiac stimulation by adrenergic hyperactivity and altered calcium homeostasis. A second mechanism manifests with normal or reduced cardiac output and elevated systemic vascular resistance due to increased vasoreactivity. Another (and overlapping) mechanism is increased salt and water reabsorption (salt sensitivity) by the kidney, which increases circulating blood volume.

**1.16 Risk factor:**

There are many things which contribute to an individual's risk of developing high blood pressure. These things are collectively called "risk factors." Many diseases have important risk factors, and high blood pressure is no exception.

**i. Age**

Being older than age 55 is an important risk factor. Simply stated, the odds of developing high blood pressure increase as we get older.

**ii. Ethnicity**

Being black is associated with a higher risk of developing high blood pressure. New studies are inconclusive on whether the risk is equivalent between African Americans and people of African heritage who have never left the African continent.[29]

**iii. Gender**

At younger ages, women are less likely to develop high blood pressure than men. This risk equalizes later in life, but statistically, women are still less likely to develop high blood pressure, overall.

**iv. Family History**

Having a family history of high blood pressure places you in a higher risk category than someone with no family history of high blood pressure. However, what this *actually* means is still a topic of research. It is clear that family history plays an important role in determining risk, but there are probably more important factors, and they are under your control.[30]

**v. Smoking**

Smoking is the number 1 risk factor over which you have control. Smoking is such a powerful risk factor for so many different human diseases that doctors are encouraged to ask every patient who smokes if they would like to quit every time they visit the office! Quitting smoking is the best thing you can do for your health.

**vi. Activity Level / Exercise**

A low exercise lifestyle leads to a weak heart, poor exercise tolerance, and obesity. All of which have been implicated in the development of high blood pressure.

**vii. Diet**

While there is evidence that specific items, such as salt, can worsen high blood pressure in certain individuals, the main impact that diet plays in high blood pressure risk is that it is a big factor in how much you weigh.

**viii. Medications and Street Drugs**

Certain medications can cause or worsen high blood pressure, as can a wide variety of street, or "recreational" drugs, like cocaine, crack, and amphetamines ("speed").

**ix. Kidney Problems**

The kidneys are very important regulators of long term blood pressure, and damage to the kidneys such as can occur from diabetes almost invariably leads to high blood pressure.

**x. Other Medical Problems**

Hormone imbalances, certain anatomic abnormalities, tumors, and other medical problems can cause a type of high blood pressure known as secondary hypertension.

**1.17 Diagnosis**

Hypertension is generally diagnosed on the basis of a persistently high blood pressure. Usually this requires three separate sphygmomanometer measurements at least one week apart. Diagnosis often entails three separate visits to the physician's office. Initial assessment of the hypertensive patient should include a complete historyand physical examination. Exceptionally, if the elevation is extreme, or if symptoms of organ damage are present, then a diagnosis may be made and treatment started immediately.

Once the diagnosis of hypertension has been made, physicians will attempt to identify the underlying cause based on risk factors and other symptoms, if present. Secondary hypertension is more common in preadolescent children, with most cases caused byrenal disease. Primary or essential hypertension is more common in adolescents and has multiple risk factors, including obesity and a family history of hypertension. Laboratory tests can also be performed to identify possible causes of secondary hypertension, and to determine whether hypertension has caused damage to the heart, eyes, and kidneys. Additional tests for diabetesand high cholesterol levels are usually performed because these conditions are *additional risk factors for the development of heart disease and require treatment.*[31] *Typical* tests are classified as follows:

| System | Tests |
|---|---|
| Renal | Microscopic urinalysis, proteinuria, serum BUN (blood urea nitrogen) and/or creatinine |
| Endocrine | Serum sodium, potassium, calcium, TSH (thyroid-stimulating hormone). |
| Metabolic | Fasting blood glucose, total cholesterol, HDL and LDL cholesterol, triglycerides |
| Other | Hematocrit, electrocardiogram, and chest radiograph |

Creatinine (renal function) testing is done to assess the presence of kidney disease, which can be either the cause or the result of hypertension. In addition, creatinine testing provides a baseline measurement of kidney function that can be used to monitor for side effects of certain antihypertensive drugs on kidney function. Additionally, testing of urine samples forprotein is used as a secondary indicator of kidney disease. Glucosetesting is done to determine if diabetes mellitus is present.Electrocardiogram (EKG/ECG) testing is done to check for evidence that the heart is under strain from high blood pressure. It may also show whether there is thickening of the heart muscle (left ventricular hypertrophy) or whether the heart has experienced a prior minor disturbance such as a silent heart attack. A chest X-ray may be performed to look for signs of heart enlargement or damage to heart tissue.

### 1.18 Treatment of Hypertension in Patients with Diabetes Mellitus:

#### 1.18.1 General Goals of Therapy

No large, population-based, randomized trials of hypertension treatment in diabetic patients have been conducted. Nevertheless, as proposed by a recent consensus statement,[32] the goal of treating hypertension in diabetic patients should be to prevent death and disability associated with high BP. In addition, other reversible risk factors for cardiovascular disease need to be addressed. For example, target-organ involvement should be considered when a treatment plan is being formulated. The major focus of clinical and investigative efforts has been on retarding the progression of diabetic nephropathy (see below) and to a lesser extent

reducing cardiovascular morbidity and mortality. The diagnosis of hypertension should be based on multiple BP measurements obtained in a standardized fashion on at least three occasions. Supine, sitting, and standing BPs should be measured in all diabetic patients. Automated ambulatory BP monitoring may be especially helpful in the diabetic patient for evaluating BP control over a 24-hour period to document the absence of the usual nocturnal fall in BP in diabetes (especially with autonomic dysfunction or nephropathy). Ambulatory BP monitoring may also be useful in documenting episodic hypertension, orthostatic hypotension, or resistant hypertension, which are relatively common in diabetic individuals with accompanying hypertension.[32]

### 1.18.2 Blood pressure goal in diabetes with hypertension

Although the optimal BP level during antihypertensive treatment in patients with diabetic nephropathy has not been defined, a review of the relationship between the rate of fall in GFR and the BP level during antihypertensive treatments suggests that we should strive for lower goal BP than recommended by current guidelines.[32,33] First, the benefit of reducing BP has been demonstrated most clearly when treatment is instituted before GFR is markedly reduced.[33] This emphasizes the concept that efforts to reduce BP should begin before serum creatinine is elevated. Second, the best results apparently have been achieved by reducing BP below conventionally accepted levels.[32,33] Indeed, the smallest decline in renal function is found in patients with BP levels around 130/85 mm Hg, a level that is readily attainable during treatment in incipient diabetic nephropathy before the decline in GFR has started. This is also the goal of BP attainment recommended in a recent consensus.[33, 33]

### 1.18.3 Nonpharmacological Therapy in Diabetic Hypertensive Patients

Lifestyle modifications may serve as definitive therapy for mild hypertension in diabetic patients or as an adjunct to pharmacological therapy to lower the number and dose of antihypertensive drugs.[32] The diet recommended by the American Diabetes Association, which is low in calories and fat, high in carbohydrate and soluble fiber, and moderately low in protein, has been reported to lower BP in diabetic patients.[32] Moderate salt restriction reduces systolic BP, which is often inordinately elevated in diabetic patients.[32] Weight reduction is important, particularly in type II diabetics, and improves glucose tolerance as

well as reducing BP.[32] For example, for each 10-lb weight reduction, systolic and diastolic pressures can be expected to decrease by 10 and 5 mm Hg, respectively.[32] Moderate but regular aerobic exercise improves glycemic and lipemic control and helps with weight reduction.

Results of the Diabetes Control and Complications Trial (DCCT), a 7-year study of more than 1440 patients, demonstrated that intensive insulin therapy reduced the occurrence of microalbuminuria by 39% and that of albuminuria by 54%. In addition, intensified therapy patients had lower rates of serious retinopathy requiring photocoagulation, lower rates of decreased visual acuity, and fewer cases of nephropathy. Similar results were reported from a study designed to test the hypothesis that optimized glycemic control in type I diabetic recipients of renal allografts will prevent or delay diabetic renal lesions in the allograft. This study was a prospective, controlled, and randomized trial of glycemic control in an inception cohort (ie, all patients were at stage 0 for diabetic renal lesions in the graft when randomized to the trial) of type I diabetic renal allograft recipients. The experimental group had maximized glycemic control, and the standard group received standard clinical diabetic care. Patients underwent baseline (before transplant) and 5-year post-transplant allograft biopsies. More than a twofold increase in the volume fraction of mesangial matrix per glomerulus occurred, as well as a threefold increase in arteriolar halitosis, greater widening of the glomerular basement membrane and increase of volume fraction of the total mesangium in the patients receiving standard treatment compared with those with maximized glycemic control. This trial indicates a causal relationship between hyperglycemia and an important lesion of diabetic nephropathy, mesangial matrix expansion, in renal allografts transplanted into diabetic recipients. In summary, newly available data suggest that aggressive control of blood sugar in the very early stages of this disease process can provide significant protection against its development.

Prospective clinical trials in type I diabetic patients with overt nephropathy showed that even with moderate protein restriction, renal function is stabilized in diabetic nephropathy. Although both studies were limited to diabetic patients with overt nephropathy, it has been suggested that dietary protein restriction will produce even better results if implemented during the early stages of diabetic nephropathy. In recognition of these data, the American

Diabetes Association has recommended that dietary protein be restricted to 0.8 g/kg body wt per day in all patients with diabetes other than children and pregnant or lactating women. It is still unclear to what extent dietary protein intake needs to be restricted to obtain maximal effects on delaying the progression of renal disease, but without producing metabolic side effects or malnutrition. For most diabetic patients, restricting dietary protein to 0.8 g/kg body wt per day would constitute a significant but practical reduction of their usual protein intake and would be likely to have a beneficial effect. Patients are also more likely to adhere to moderately protein-restricted diets than to more drastic restrictions.

### 1.18.4 Blood Pressure Control and Progression of Diabetes Nephropathy

Hypertension invariably complicates the course of patients with diabetic nephropathy. Of the 35% to 40% of either IDDM or NIDDM patients who ultimately develop nephropathy, all at some time in their natural history will be hypertensive.[32] Numerous clinical trials of both IDDM and NIDDM hypertensive patients with nephropathy have assessed diverse forms of BP-lowering therapy on the progression of renal disease.[32,33] These trials have all demonstrated that aggressive reduction of an elevated BP to levels below 140/90 mm Hg will retard the progression of diabetic renal disease. Furthermore, recent data suggest that some antihypertensive drugs may confer unique beneficial effects in attenuating the progression of this disease independent of their BP-lowering effects. [32 33]

### 1.18.5 Pharmacological Treatment of Hypertension in the Diabetic Patient

Pharmacological therapy should be initiated when lifestyle modifications are unsuccessful in controlling hypertension in the diabetic individual.[32] The National Institutes of Health Consensus Panel recommended four classes of drugs that are effective as first line single agent therapy.[33] Each drug class has potential advantages and disadvantages. Recent data from several large scale hypertension treatment trials suggest that some classes may be preferred in the diabetic patient with nephropathy, and these considerations will be addressed. The five major classes of antihypertensive drugs currently being used in the United States for the diabetic hypertensive patient are discussed below.

### 1.18.6 ACE Inhibitors

ACE inhibitors have no adverse effects on lipid levels or glycemic control.[32] Experimental studies have provided a theoretic framework for anticipating that ACE inhibition may preferentially retard the progression of diabetic renal disease. Studies over the past decade have demonstrated that the sustained increase in glomerular capillary pressure evoked in response to loss of renal mass produces a destructive sclerosing reaction. Administration of ACE inhibitors decreases glomerular capillary pressure, with a resultant reduction of glomerulosclerosis, suggesting that ACE inhibitor therapy may protect the injured kidney from hemodynamically mediated glomerular damage.

The results of the first major attempt to compare patients randomized to an ACE inhibitor or alternative therapy were reported in 1992 from a study of 40 patients with IDDM and diabetic nephropathy randomized to treatment with either enalapril or metoprolol, generally combined with furosemide. Treatment with enalapril compared with metoprolol resulted in a highly statistically significant reduction in the rate of decline of GFR and in the level of proteinuria. Overall, there was no statistical difference in the BP reduction or BP achieved with the two treatments. Recently, the Diabetes Collaborative Study Group reported the results of a trial designed to determine whether the ACE inhibitor captopril is more effective in slowing the progression of diabetic nephropathy than are agents that act primarily by reducing BP. This was a randomized, controlled trial comparing captopril with placebo in patients with IDDM in whom urinary protein excretion was greater than or equal to 500 mg/d and serum creatinine concentration was less than or equal to 2.5 mg/dL. The BP goal was to achieve BP control during a median follow-up of 3 years. The primary end point was a doubling of the baseline serum creatinine concentration. Serum creatinine concentrations doubled in 25 patients in the captopril group compared with 43 patients in the conventional therapy group. The reduction in the risk of a doubling of serum creatinine concentration was 48% in the captopril group as a whole. Captopril therapy was associated with a 50% reduction in the risk of the combined end points of death, dialysis, and transplantation that was independent of the small disparity in BP between the groups. In a recent subgroup analysis of the data, remission of nephrotic-range proteinuria was observed in 7 of 42 patients assigned to captopril (16.7%; mean follow-up, 3.4±0.8 years) but in only 1 of 66

patients assigned to placebo. The findings were interpreted as suggesting that both BP control and reduced proteinuria contribute to the reduced rate of GFR loss in the remission group.

Whereas most available clinical trials have assessed the effects of ACE inhibition in patients with IDDM, recent clinical trials in NIDDM patients have been reported. A long-term 5-year study evaluating the effects of ACE inhibition on proteinuria and on the rate of decline in renal function in NIDDM patients with microalbuminuria was recently conducted in Israel.[25] In a randomized, double-blind, placebo-controlled trial of 94 patients ACE inhibition during the early stages of diabetic nephropathy resulted in long-term stabilization of plasma creatinine levels and of the degree of urinary loss of albumin. Lebovitz et al recently reported the results of a 3-year prospective, double-blind, placebo-controlled trial in NIDDM patients and demonstrated that an antihypertensive regimen that included the ACE inhibitor enalapril preserves renal function to a greater extent than does therapy with antihypertensive agents excluding ACE inhibitors. The rate of loss of GFR was significantly greater in patients with overt proteinuria at baseline (urinary albumin excretion >300 mg/24 h) compared with patients with baseline subclinical proteinuria (urinary albumin excretion ≤300 mg/24 h). Antihypertensive treatment with enalapril preserved GFR better in the patients with subclinical proteinuria at baseline than the other antihypertensive treatments that excluded the ACE inhibitor. Furthermore, only 7% of the enalapril-treated group progressed to clinical albuminuria compared with 21% of control patients. On the basis of these findings these investigators suggested that ACE inhibitors should be used as initial treatment for hypertensive NIDDM patients with or without microalbuminuria and not held in reserve until clinical albuminuria or proteinuria develops.

An important meta-regression analysis of the relative effects of different antihypertensive agents on proteinuria and renal function in patients with diabetes was recently reported. This analysis assessed 100 controlled and uncontrolled studies that provided data on renal function, proteinuria, or both before and after treatment with an antihypertensive agent. Multiple linear regression analysis indicated that ACE inhibitors decreased proteinuria independent of changes in BP, treatment duration, and type of diabetes or stage of nephropathy. It was concluded that ACE inhibitors had a unique ability to decrease proteinuria independent of the reduction in proteinuria caused by changes in systemic BP.

Despite these promising results, several caveats are in order. Lowering of BP per se may be the major factor contributing to the salutary renal effects of ACE inhibitors as well as other antihypertensive agents in patients with diabetes and hypertension.[35] ACE inhibitors are not free of side effects. An infrequent but important risk of ACE inhibitors is an acceleration of renal insufficiency, particularly in patients with bilateral renal artery stenosis and possibly more commonly in patients with diabetes. Under conditions in which filtration pressure depends on angiotensin II, the converting enzyme inhibitors may cause a precipitous fall in GFR. This complication is most likely to occur in the presence of bilateral renal artery stenosis due to atheromatous plaques or severe congestive cardiac failure. ACE inhibitors may provoke hyperkalemia, particularly in those individuals with decrements in GFR.[32] Finally, care must be exercised in initiating ACE inhibitor therapy in patients receiving diuretics because BP may drop and renal function decline profoundly.[32]

### 1.18.7 Calcium Antagonists

The published studies regarding calcium antagonists and diabetic renal disease have been widely divergent in their design and findings.[35,36]The Melbourne Diabetic Nephropathy Study Group has reported the 24-month results of their prospective, randomized study comparing the effects of the ACE inhibitor perindopril with those of the calcium antagonist nifedipine on BP and microalbuminuria in 43 diabetic patients with persistent microalbuminuria. After 12 months of therapy the investigators observed that both drug regimens were equally efficacious in reducing BP and albumin excretion in hypertensive patients. However, the 2-year follow-up data demonstrated that proteinuria had returned to baseline in the nifedipine-treated group but remained decreased in the perindopril-treated group. Thus, more long-term prospective studies need to be conducted to determine the benefits of both dihydropyridine and nondihydropyridine calcium antagonists in patients with hypertension and associated diabetic nephropathy.

In addition, it has been suggested that the combination of a calcium antagonist with a converting enzyme inhibitor should result in a greater reduction in urinary protein excretion and slowed morphological progression of nephropathy. One study compared the renal hemodynamic and antiproteinuric effects of a nondihydropyridine calcium antagonist and an

ACE inhibitor alone and in combination in NIDDM patients with documented nephrotic range proteinuria, hypertension, and renal insufficiency. Patients treated with the combination of a calcium antagonist and ACE inhibitor manifested the greatest reduction in albuminuria. In addition, the decline in GFR was the lowest in this group. Although such an approach is extremely attractive, additional studies will be required to extend these initial observations.

### 1.18.8 Thiazide Diuretics

Thiazide diuretics in small doses are used frequently and successfully to treat hypertension in individual diabetic patients.[32] These drugs have been shown to reduce cardiovascular morbidity and mortality in large population-based randomized trials (Systolic Hypertension in the Elderly Program [SHEP]). If the dose is low (ie, 25 mg or less hydrochlorothiazide or chlorthalidone daily), adverse effects on carbohydrate metabolism, hypokalemia, and hypomagnesemia are uncommon. Because the diabetic hypertensive patient is generally volume expanded, diuretics are often necessary for adequate control of BP. The disadvantages of thiazides are that they cause short-term dyslipidemia, altered carbohydrate metabolism, hypokalemia, hypomagnesemia, and hyperuricemia in some patients, but these adverse effects are minimized at the low doses recommended.[32] Diuretics are also very useful antihypertensive agents when used in conjunction with ACE inhibitors; this combination is often synergistic in lowering BP and minimizes the metabolic side effects of diuretics.

### 1.18.9 ß-Blockers

Several concerns limit the usefulness of ß-blockers in treating people with diabetes: (1) these agents may have adverse effects on glucose and lipid metabolism. (2) Most troublesome for the insulin-treated diabetic subject is the observation that ß-blockers can interfere with awareness of hypoglycemia in patients with diabetes and perhaps also prolong the recovery from hypoglycemia.[32] The catecholamine-mediated symptoms of hypoglycemia-induced symptoms can be blunted if not abolished. The reflex tachycardia that serves to warn the patient of hypoglycemia may be blocked, putting the patient at greater risk of progressing to central nervous system symptoms. (3) ß-Blockers can reduce peripheral blood flow and

worsen claudicating and vasospasm in patients who already have a compromised peripheral vascular system. (4) Finally, when ß-blockers are added to diuretics, an aggravation of the hyperglycemic effect of the latter may occur.[32] Results from a recent investigation suggest that obese elderly patients treated with ß-blockers and diuretics were at greater risk of developing NIDDM compared with obese elderly normotensive individuals. Thus, except under special circumstances (eg, in the presence of angina pectoris and after myocardial infarction), ß-blockers should no longer be used as first-line antihypertensive medications in these patients.

### 1.18.10 $\alpha_1$-Blockers

$\alpha_1$-Blockers have been recommended for the treatment of diabetic hypertension on the basis of their efficacy, lack of adverse effects on glucose or insulin metabolism, and neutral or perhaps beneficial effect on the lipid profile.[32] These agents infrequently produce or exacerbate sexual dysfunction and may permit improvement of sexual function when substituted for a central sympatholytic agent.[32] Currently, there is no reported clinical evidence that peripheral α-blockers aggravate diabetic orthostatic hypotension, as is said to be the case with centrally acting sympatholytics.[32]

There are both advantages and disadvantages to the use of central sympatholytic antihypertensive agents (eg, clonidine, guanabenz, methyldopa, guanfacine) in the diabetic patient. Advantages include their lipid-neutralv[32] and minimal-to-absent hyperglycemic effects.[32] However, centrally acting sympatholytic medications may worsen or unmask both orthostatic hypotension and sexual dysfunction in diabetic patients.[32] In summary, although central sympatholytic agents have few if any metabolic side effects, some of their putative other adverse effects render them less than ideal antihypertensive agents for the management of diabetic patients.

### 1.19 Diabetes with hypertension

Diabetes and high blood pressure are related diseases that feed one another and tend to get worse with time. In biological terms, the relationship between diabetes and high blood pressure is a type of positive feedback loop, where one step causes a second step and that second step "feeds back" to cause more of the first step.

The well-studied example of the self-reinforcing relationship between diabetes and high blood pressure takes place in the kidneys. The kidneys are the body's most important long-term blood pressure regulator. By balancing the amount of salt and potassium in the body, the kidneys ultimately control how much fluid is excreted as urine. This fluid regulating function helps modulate long-term blood pressure by physically controlling how much liquid is present in the blood vessels. Carrying out this function depends on a constant flow of blood across delicate capillarystructures known as glomeruli (singular: glomerulus). The glomeruli are the filtering units of the kidney.

The high blood sugar levels associated with diabetes damage capillaries, including those that comprise the glomeruli. Through a complex series of steps, excess blood sugar actually causes the walls of capillaries to thicken and, in some cases, degrade entirely. While the precise mechanisms underlying this process are too complicated to discuss in detail, the end result is that the glomeruli become thicker, and are tricked into thinking that they aren't receiving enough blood. As a result, the kidneys respond by raising blood pressure to restore "normal" blood flow through the glomeruli. Because they have been damaged, the glomeruli essentially require a permanent increase in blood pressure in order to continue filtering the blood. As time goes on, continued exposure to elevated sugar damages the glomeruli more, leading to ever increasing blood pressures as the kidneys try to correct the situation.

These elevated blood pressures have widespread effects on the other organ systems of the body, including the muscles and insulin secreting areas of the pancreas. In the muscles, higher pressure causes blood vessels to contract. As a result, less blood flows through the large muscle areas of the body. This leads to a decrease in the size of muscle cells and a decrease in the amount of sugar that those cells absorb from the blood. Because less sugar is being absorbed from the blood, the level of free sugar in the blood rises. This free sugar

ultimately makes its way to the kidneys, where it contributes to further glomerular damage. Altered blood flow through the pancreas, as a result ofautoregulation, can also lead to a decrease in insulin production, raising the blood sugar even higher.

Because diabetes and high blood pressure are so strongly self-reinforcing, it is vitally important to maintain tight control of both blood sugar and blood pressure. Even modest elevations of either in patients suffering from both diseases can quickly lead to an exaggerated amount (an "amplified" amount) of damage. This is the primary reason that treatment goals for blood sugar are more rigorous in the setting of high blood pressure and treatment goals for blood pressure are more rigorous in the setting of diabetes. [10]

# Chapter 2

# Objective

## Hypothesis and objective of this study

**Hypothesis:** Hypertension is a potential risk factor of diabetes.

**General Objective**: Diabetes and its association with hypertension among the patients in Bangladesh.

**Specific Objective:**

The objective of this study is:

- To observe the type of disease.
- To determine the distribution of hypertension among the diabetic patients.
- To ascertain the drug resume of the diabetic patients.
- To observe the management of diabetic disease.
- To ascertain other complication of patients while they are under treatment.
- Drug used in the treatment of diabetic patients.

# Chapter 3
# Materials and Method

### 3.1 Type of study

It is a discretional study attempted to establish relationship between diabetics and hypertension among the diabetic patients of different ages. In addition to this study examine relationship between diabetic and social class demography others risk factor of diabetic.

### 3.2 Place of study

The place was conducted in Bangladesh Institute of Research and Rehabilitation in Diabetes, Endocrine and Metabolic Disorders (BIRDEM). It is the largest diabetic hospitals in Bangladesh. It was established in 1980 and composed of 593 beds offering 24 hours services. This institute comprise of outdoor, emergency, highly specialist post CCU, intensive care unit, medicine surgery and have a full-fledged indoor hospitals.

### 3.3 Study population

The diabetic patients from outdoor of a diabetes hospital diagnosed by the hospitals physician.

#### 3.3.1 Inclusion criteria of the patients

i)All the patients of diagnosed age (20-70□)

ii)Both sexes irrespective of religion and occupation.

#### 3.3.2 Exclusion criteria of the patient

i) Non-diabetic patients

ii) Post-operative patient

iii) Presence of malignancy

iv)Any other chronic disease

v) Polycythemia

### 3.4 Sample size

The objective of this study was to find out the relation of diabetic and hypertension. The required sample size was taken 105.

### 3.5 Sample technique

All the patient fulfilling the above mentioned selection criteria will include,105 in this study.

### 3.6 Research instrument

An interview schedule was used for data collection. The instrument well prepared keeping in view the object, hypothesis, variables consider in this study. Minor correction, addition, exclusion and after modification which came after presetting was incorporated in the interview schedule.

### 3.7 Research equipment

i) Interview

ii) Weighing machine (Bathroom scale)

iii) Sphygmomanometer (aneroid type)

iv) Stethoscope

### 3.8 Data collection method

After explaining the purpose of the study to the respondents and obtaining their verbal consent. We interview all the respondents by using questionnaire in Bengali and using a thoroughly protested questionnaire. The questionnaire was consists of three parts.

i) General information

ii) Behavioral characteristics

iii) Consists of physical examination, reporting blood pressure, taking physical weight, clinical examination of blood sugar and laboratory test.

### 3.8.1 Blood pressure measurement

Two measurement of blood pressure was bead on each study patient with an aneroid type blood pressure machine using a standardized technique. Both the blood pressure was obtained after the subject had rested for 15 minute in lying position. The first blood pressure was recorded after obtaining sociodemographic information while the second was recorded after a brief examination. Average of the two reading of systolic blood pressure and diastolic blood pressure were used to descriptive the blood pressure of the patient.

### 3.8.2 Anthropometric measurement

Weight was measure in kg with precision 0.5 kg with a weight machine (bathroom scale)

### 3.8.3 Blood sugar:

i) FBS ii)RBS

### 3.9 Data processing and analysis

After collection each data were recorded in master sheet checked for reaching value and inconstancy and were corrected immediately. After completion of data collection it was rechecked for quality and validity.

### 3.10 Study period

Study period one year commencing started from January 2011 to December 2011.

# Chapter 4

# Results

**4.1 Gender variation among the diabetic patients:**

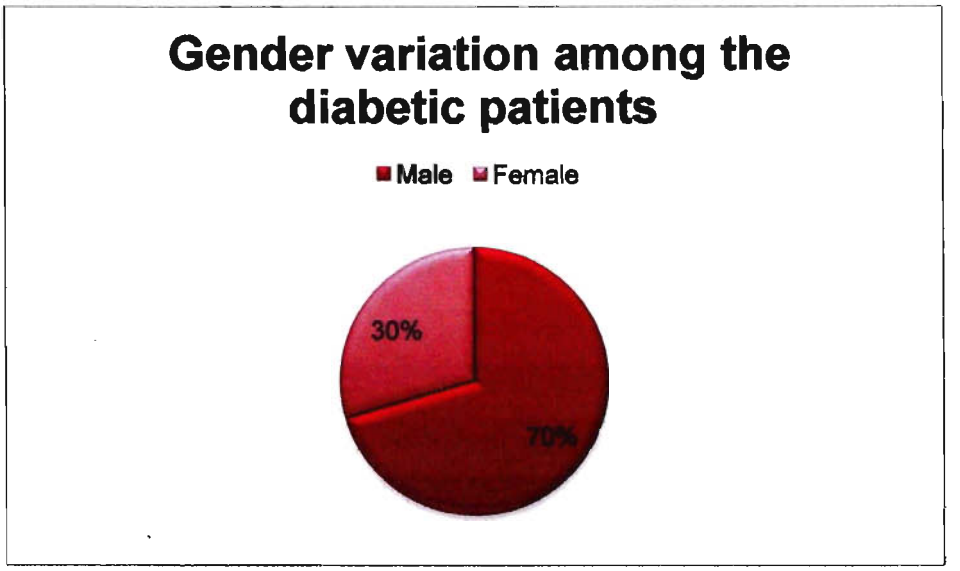



**Fig 4.1: Gender variation among the diabetic patients**

The study shows that among the 105 patients 70% patients were male and 30% patients were female having diabetes mellitus.

**4.2 Distribution of age among the diabetic patients:**

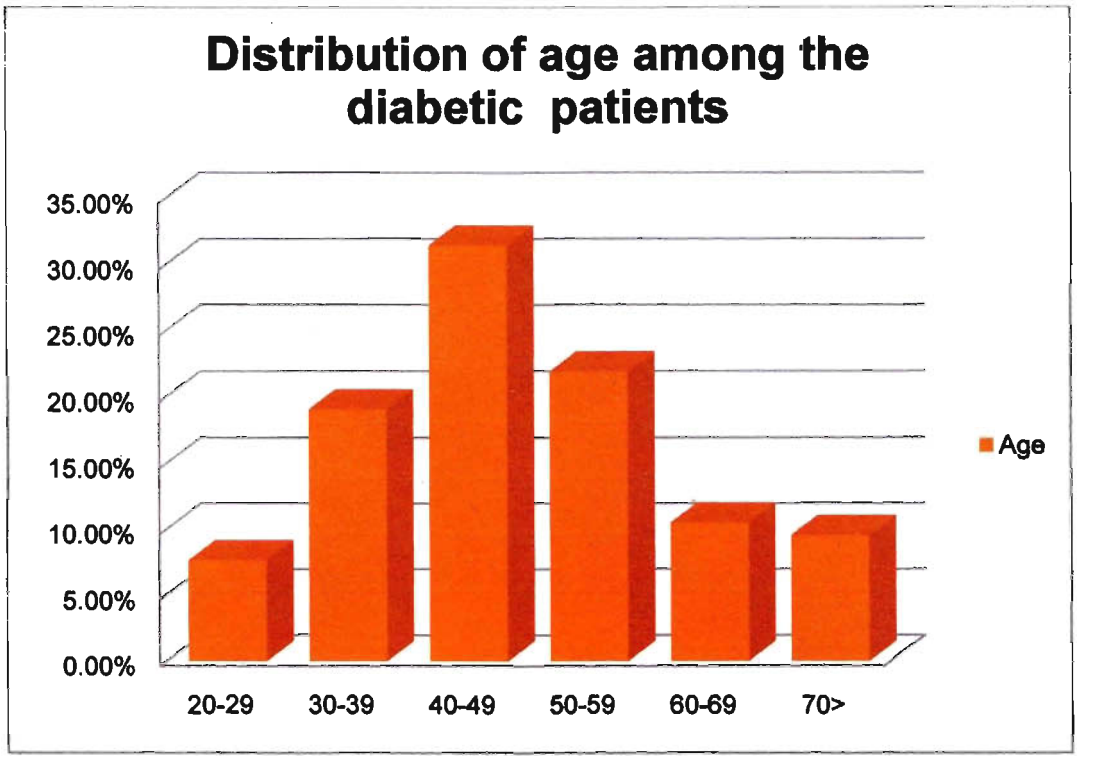



**Fig 4.2: Distribution of age among the diabetic patients**

The study show that among 105 patients of different age with diabetes mellitus where 7% patients were in 20-29 years, 19% patients were in 30-39, 31% patients were in 40-49, 21% patients were in 50-59, 10% patients were in 60-69, 9% patients were in 70>.

**4.3 Distribution of respondents by the types of diabetes:**

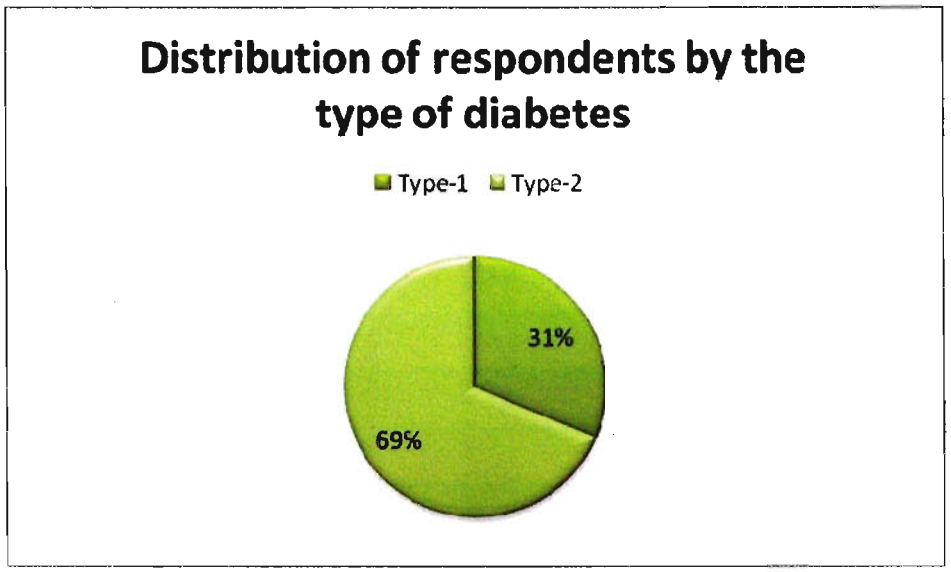



**Fig 4.3: Distribution of respondents by the types of diabetes**

The study shows that among 105 patients 69% were suffered from type-1 diabetes and 31% patients were suffered from type-2 diabetes.

**4.4 Distribution of education among the diabetic patients:**

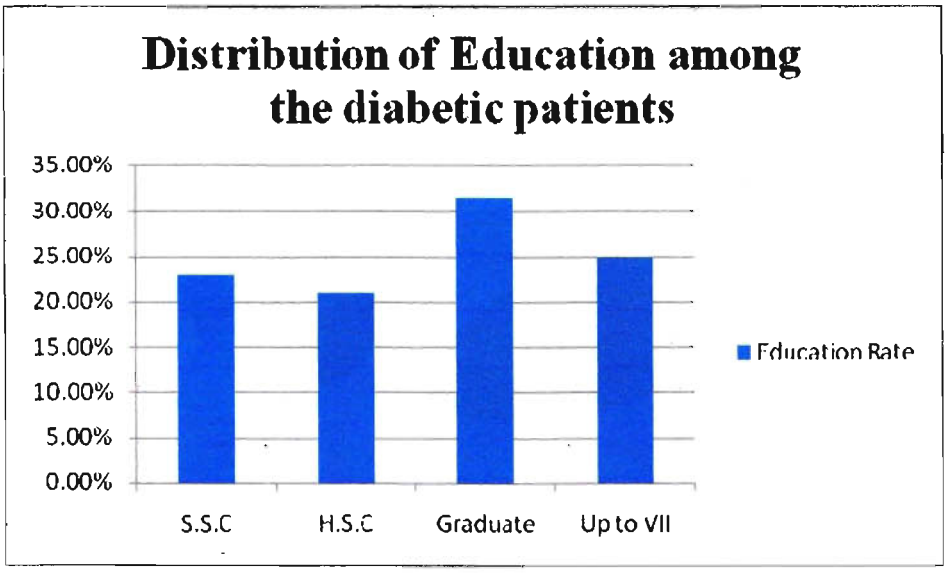



**Fig 4.4: Distribution of education among the diabetic patients**

The study shows that among 105 patients 22% patients were S.H.C pass, 20% patients were H.H.C pass, 31% patients were in graduate and 24% patients were up to VII.

**4.5 Distribution of respondents by family history of diabetes:**

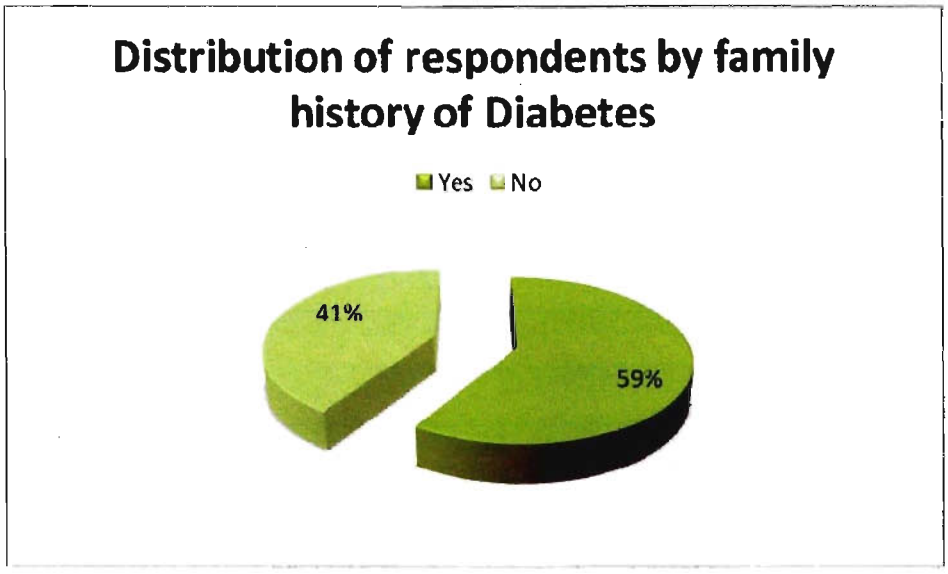



**Fig 4.5: Distribution of respondents by family history of diabetes**

The study shows that among the 105 patients 59% having diabetes of his or her family member and 41% patients have not diabetic of his or her family member.

**4.6 Distribution of respondents by smoking habit:**

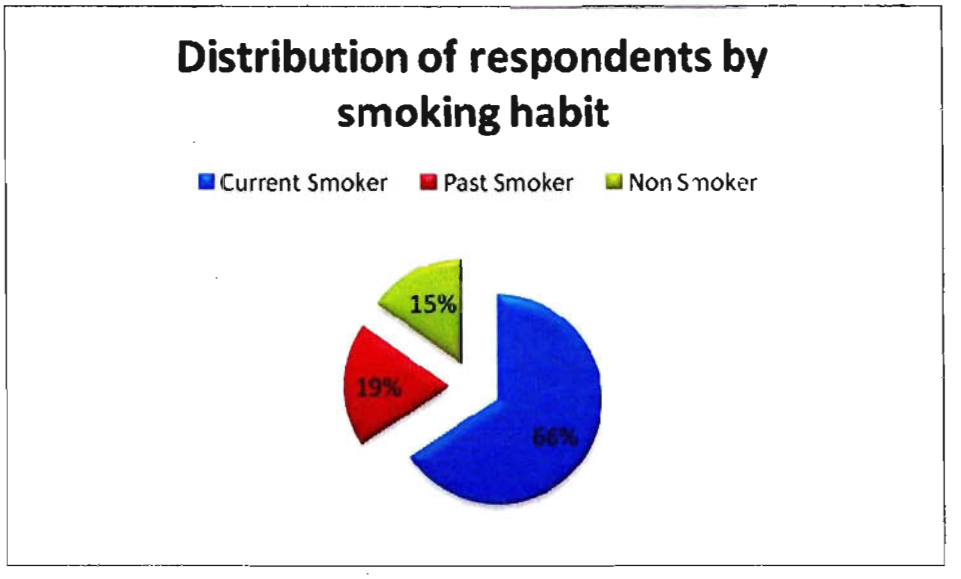



**Fig 4.6: Distribution of respondents by smoking habit**

The study shows that among the 105 patients 66% patients were current smoker, 19% were past smoker and 15% were non-smoker with diabetes mellitus.

**4.7 Distribution of respondents by taking table salt:**

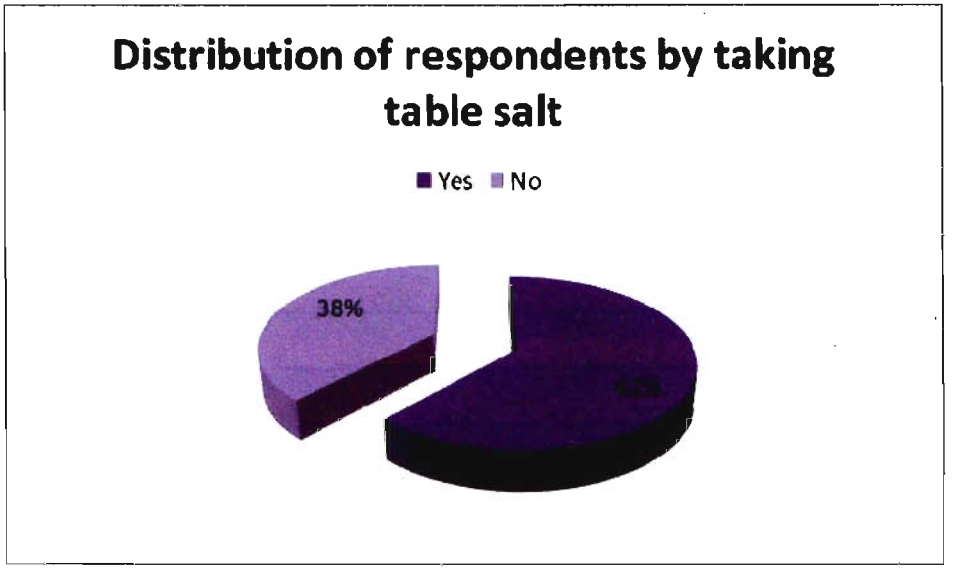



**Fig 4.7: Distribution of respondents by taking table salt**

The study shows that among the 105 patients 62% patients were consuming table salt and 38% patients were not consuming table salt.

### 3.8 Distribution of respondents by chronic disease:

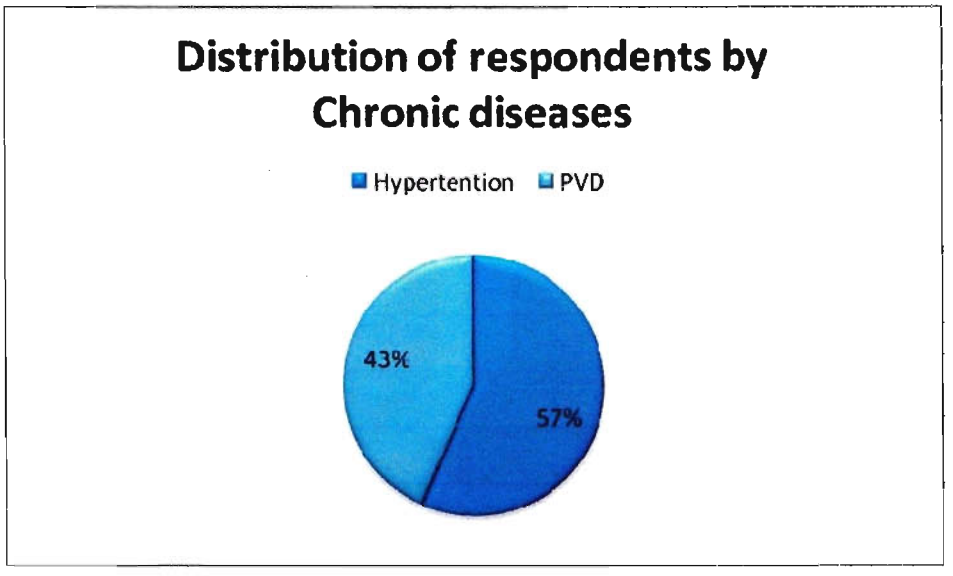



**Fig 4.8: Distribution of respondents by chronic diseases**

The study shows that among the 105 patients 57% patients were hypertensive and 43% patients were PVD with diabetic mellitus. Patients were also investigated for other chronic disease but none of them were suffering from other chronic disease like asthma, bronchitis, coronary heart disease etc.

**4.9 Distribution of eye complication among the diabetic patients:**

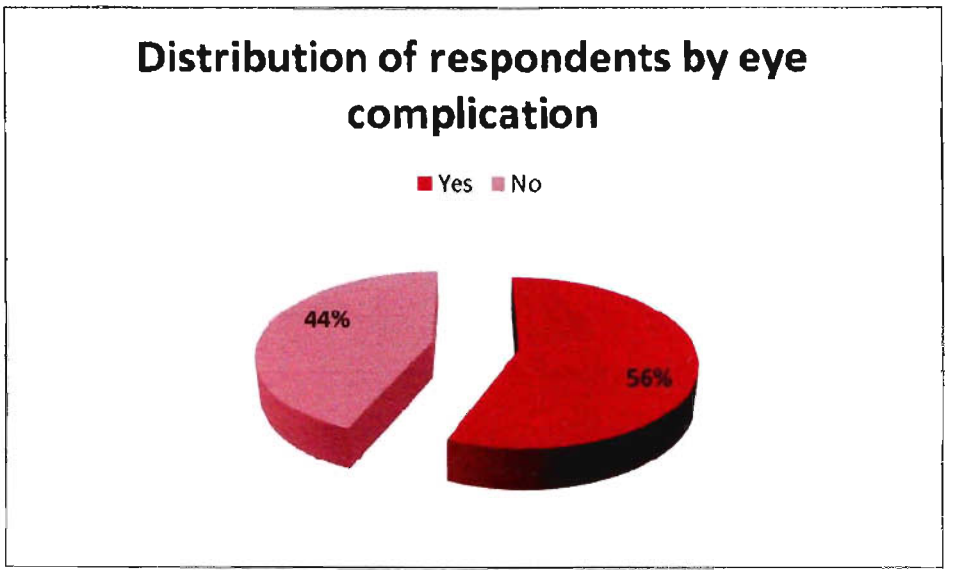



**Fig 4.9: Distribution of eye complication among the diabetic patients**

The study shows that among the 105 patients 56% patients were having eye complication and 44% were not having eye complication with diabetes mellitus.

**4.10 Distribution of respondents by doing regular exercise:**

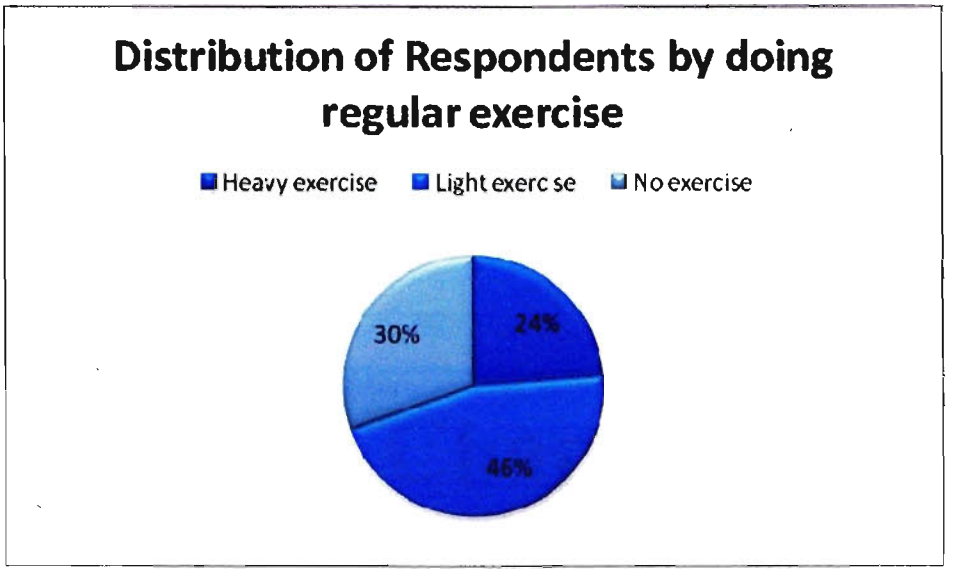



**Fig 4.10: Distribution of respondents by doing regular exercise**

The study shows that among the 105 patients 46% patients were doing light exercise, 24% patients were doing heavy exercise and 30% patients were not doing exercise.

# Chapter 5
# Discussion and conclusion

## Discussion

This is a descriptivestudy,in this study data was collected from the patients suffering from diabetes mellitus over a period of 1 year. Data were obtained from numerous sources; among patients age were between 20-70□ years. The fact from thedata obtained, the results revealed that the diabetic patients were more prone to have hypertension than the non-hypertensive patients. In addition, the distribution of risk factors like smoking, eye complicationand PVD were compared among diabetic patients. Such data are of interest in order to design and implement prevention strategies.

In this study, 105 events were recorded. Among these 74 (70%) men and 31 (30%) women were suffering from diabetic disease. Here 57% people were attacked by hypertension and 43% people were with PVD. The distribution of diabetic in type-1 (31%) and the type-2 (69%). 62% of the total population takes salt with their meal. The distribution of diabetic mellitus in different age range were collected where 40-59 years people are more in danger of suffering from diabetic mellitus. The percentage was 24% people do regular heavy exercise, 46% of the respondents do light exercise and 30% havedevoid exercise. Distribution of diabetic mellitus was more prevalent in graduate and up to VII when it was categorized based on education.

Hypertension is clearly a major public health problem. It is the one of the most important risk factors in diabetic mellitus. And smoking is another risk factor. Tobacco use is the most common cause of avoidable cardiovascular mortality worldwide. In our study we found 57% of total population was suffering from hypertension and 85% population were from smoker. Chronically, cigarette smoking induces arterial stiffness which may persist for a decade after smoking cessation. The incidence of hypertension in increased among those smoke 15 or more cigarettes per day and the coexistence of hypertension is common in diabetic mellitus patients.

## Conclusion

The aim of this survey study is to observe the present situation of diabetes disease in Bangladesh. Most of the diabetic disease occurs very silently, apparently without show any sign and symptoms. In that case at the primary state of the development of the disease some symptom can appear and symptomatic relief can be getting by taking local medication. They should consult to the expert physician. From this study it, is observed that, most of the diabetes disease occur due to the genetic factor. Aging is one of the most important factors in case of diabetes disease. As the people get older, the ability of the liver and kidney decrease gradually.

Diabetes is a metabolic disorder. It is not curable but the disease condition can be control within normal range and hypertension also manageable by proper medication, life style modification and management. Which people are suffering from the both disease simultaneously suffering becomes measurable. So proper medication, life style modification like quietly smoking, proper physical exercise, regular and timely balance diet, less fatty food consumption, control body weight, limiting mental stress can make patients healthier.

# Chapter 6

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## ANNEXURE

### Survey on Diabetic patient in hospital

(Questionnaire for the Patients)

**Interviewer's name:**

**General information:**

1. Patient's name:

2. Address:

3 Age.....year

4. Sex

a) Male b) Female

5. Religion

a) Islam b) Hinduism c) Christianity d) Others

6. Personal income

a) Less than 4000 b) 5000-10000 c) 10000-15000 d) More than 20000

7. Occupation

a) Farmer b) Businessman c) Service holder d) Unemployed

f) House wife g) others

8. Education

a) SSC b) HSC c) Graduate d) Up to class VII

9. Marital status

a) Married b) Unmarried

10. How many years, you are suffering from diabetic diseases?

a) Less than 2 years b) 2-5 years c) More than 5 years

11. Any of your family members have following disease?

Hypertension/ Diabetic/ CHD/ PVD

a) Yes b) No

12. What is the relation between you and them?

a) Father b) Mother c) Both d) Siblings

13. Did you ever smoke any time in your life?

a) Yes b) No

14. Do you currently smoke?

a) Yes b) No

15. How much do you smoke?

a) Everyday b) Occasionally

16. What type cigar do you smoke?

a) Cigarette b) Biri c) Both d) Others

17. How much you daily consumed (number of stick)?

a) Less than 10 b) 10-15 c) 15-20 d) More than 25

18. Do you take Tobacco leaf?

a) Yes b) No

19. How much do you chew betel nut?

a) Everyday b) Occasionally

How many times you taken?

a) Once b) Twice c) 3-5 d) More than 5

20. Do you take nonsmoking tobacco?

a) Jorda powder b) Tobacco leaf c) Both d) Gual

21. Do you take table salt?

a) Yes b) No

22. Do you take alcohol?

a) Yes b) No

If yes, what's your consuming period?

a) Before 2 years b) Currently

23. Are you suffering from following chronic disease?

a) Hypertension b) CHD c) PVD d) Bronchitis e) Asthma

24. Are you suffering from any eye complication?

a) Yes b) No

25. Your weight and height?

Ans: .....cm

26. What is your blood group?

.....

27. Blood urea.....

28. Serum electrolyte

a) Na.....m.eq/L

b) K.....m.eq/L

29. RBS

30. FBS

31. ECG report

32. X- ray chest:

33. Systolic blood pressure.....mmHg

34. Diastolic blood pressure.....mmHg

35. Are you recently checked your lipid profile?

a) Yes b) No

If yes-

i.TC:

ii.TG:

iii.HDL:

iv.LDL:

36. Are you doing any physical activity to control your diabetics?

a) Yes b) No

If yes, what is your professional status in physical activity?

a) Secondary b) Involved in regular exercise

If you involved in regular exercise, which type of exercise are you doing?

a) Light b) Heavy c) Moderate

37. Are you suffering from any leg problem?

a) Yes b) No

If yes, which types of problem you have?

a) Pain b) Pain during walking c) Remission after stop walking

d) Blacking finger and toe e) Gangrene

38. Do you know which type of diabetics you have?

a) Yes b) No

39. Which type of medication you taken to control diabetics?

a) Diet and exercise b) insulin c) oral anti diabetic drug

If you taking insulin-

Dose.....mg.....times daily

If you taking oral anti diabetic drug-

Dose.....mg.....times daily for.....days

**40. Other drugs:**

i. Antihypertensive

ii. Antiarrhythmic

iii. Antiangina

iv. Lipid lowering agent

v. Antidiabetic

vi. Steroid

vii. Anti-platelet

viii. Anticoagulant

ix. Others