Prevalence of Type 2 Diabetes Mellitus complications in human

Dr. Md. Minhazul Alam

Roll no. 0119/06

Registration No. 733

Session: 2019-2020

A thesis submitted in the partial fulfillment of the requirements for the degree of Masters of Science in Public Health

One Health Institute

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This is to certify that, we have examined the above Master's thesis and have found that is complete and satisfactory in all respects, and that all revisions required by the thesis examination committee have been made.

Prof. Dr. S. K. M Azizul Islam **Supervisor** **Professor & Head** **Department of Physiology, Biochemistry & Pharmacology,** **CVASU**	**Prof. Dr. Sharmin Chowdhury** **Director** **One Health Institute**

One Health Institute
Chattogram Veterinary and Animal Sciences University
Chattogram- 4225, Bangladesh,
June 2021

I dedicate this precious work

to my beloved parents, my wife, my sons and

my all respected teachers

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The Author

June 2021

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List of Abbreviations

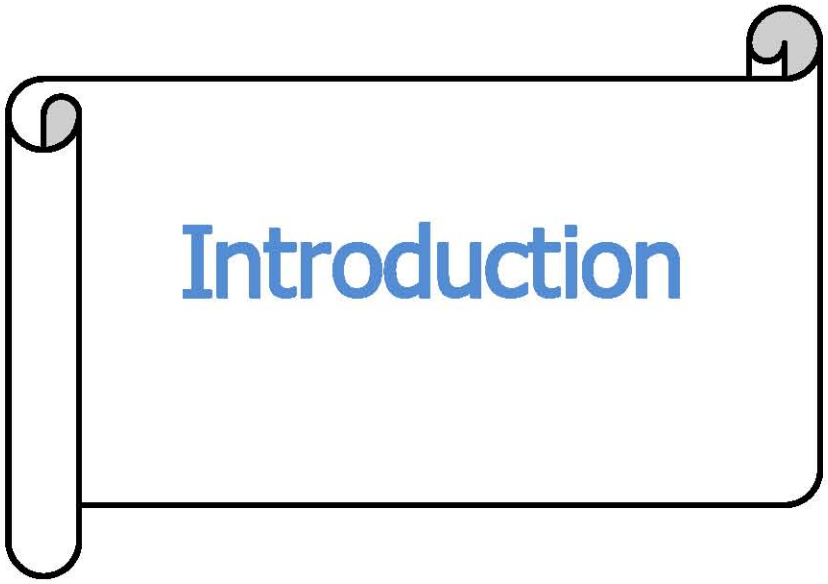
Abbreviation	Elaboration
ADA	American Diabetic Association
BMI	Body Mass Index
BP	Blood Pressure
CDGH	Chattogram Diabetic General Hospital
cm	Centimeter
COVID	Corona Virus Disease
COX	Cyclooxygenase
CSMO	Clinically Significant Macular Oedema
CVD	Cerebrovascular Disease
DBP	Diastolic Blood Pressure
DKA	Diabetic Ketoacidosis
DNA	Deoxyribonucleic Acid
DPP	Dipeptidyl peptidase
DR	Diabetic Retinopathy
FPG	Fasting Plasma Glucose
GBD	Global burden of Disease
GDM	Gestational Diabetes Mellitus
GIT	Gastrointestinal tract
gm	Gram
HbA1C	Glycosylated Hemoglobin
HDL	High Density lipoprotein
HSC	Higher Secondary Certificate
HTN	Hypertension
IHD	Ischemic Heart Disease
IDF	International Diabetic Federation
IDL	Intermediate density lipoprotein
Kg	Kilogram
LDL	Low Density Lipoprotein

mg/dl	Milligram per deciliter
NAD(P)H	Nicotinamide Adenine Dinucleotide Hydrogen Phosphate
NCD	Non-communicable disease
NIDDM	Non-insulin-dependent diabetes mellitus
NOS	Nitric Oxide Synthase
NPDR	Non Proliferative Diabetic Retinopathy
OAD	Oral Anti-diabetic Drug
OGTT	Oral Glucose Tolerance Test
OPD	Outpatient door
RAAS	Renin Angiotensin Aldosterone System
RNA	Ribonucleic Acid
SBP	Systolic Blood Pressure
SD	Standard Deviation
SGLT	Sodium-Glucose Transport protein
SGPT	Serum Glutamic Pyruvic Transaminase
SMCH	Southern Medical College Hospital
SSC	Secondary School Certificate
T2DM	Type 2 Diabetes Mellitus
TG	Triglycerides
TLR	Toll Like Receptors
TSH	Thyroid Stimulating Hormone
u/L	Unit per Liter
US$	United States Dollar
VLDL	Very low-density lipoprotein
WHO	World Health Organization

Abstract

Type 2 Diabetes Mellitus (T2DM) is chronic metabolic disorder imposes social and economic burden, which has increased worldwide manifolds with high morbidity and mortality in both developed and developing countries. Since it is a chronic disease, it can cause complications if remain uncontrolled. The aim of the study was to find out the socioeconomic status, diabetic complications and associated risk factors with their prevalence and anti-diabetic therapy. A Cross sectional study was carried out for a period of one year (October 2020 to October 2021) among the diagnosed T2DM patients in Southern Medical College Hospital (SMCH), Chattogram Diabetic General Hospital (CDGH) and author's personal chamber. Total 158 patients were enrolled for this study and data were collected through a pre-structured questionnaire. Collected data were entered into the MS Excel-2010, sorted out and exported to Statistical Package for Social Sciences (SPSS) version20.0. Descriptive statistics were performed followed by student t test and Chi-square test among different groups then correlation and multiple linear regression analysis were performed. Among total enrolled 158 patients, 46% were male and 54% were female where 62% patents lived in urban. Significant 50% patients didn't do any job and 50% were HSC and above. 13.3% patients didn't do any daily exercise with 27% lead sedentary life style and 61.4% had daily sunlight exposure varying from few hours to 6-8 hours. Female has a higher BMI (Body mass index) with 95% *CI* 25.76~27.06 (p=.001). Systolic blood pressure was higher in female than male according to duration (p=.026). 29.70% patients use insulin as anti-diabetic therapy. Microvascular complications of T2DM, Diabetic retinopathy symptoms (eye problems, 38.60%), diabetic neuropathy symptoms [Paraesthesia (Burning sensation, 36.07%), Periodontitis/Teeth and gum problem (36.70%), Gastrointestinal problems (24.05%), Sexual dysfunction (9.50%), Psychological problems (1.26%) and Diabetic nephropathy (Kidney problems, 8.22%)] were found in the study. Macrovascular complications of T2DM, Ischemic Heart Disease (20.88%) and Cerebrovascular disease (2.53%) were found in this study. T2DM closely associated risk factors like hypertension and Dyslipidemia was found in 54.44% and 44.30% patient respectively. Male-female correlation of T2DM complications and associated factors was negatively significant regarding Teeth/Gum problems (p= -.348**) for daily sunlight exposure. Chi-square test showed increase prevalence ($p<0.05$) for HTN and Dyslipidaemia regarding daily exercise; Hypertension, CVD, Diabetic neuropathy (Paraesthesia, periodontitis, Feet/Leg cramps, GIT problems) and Kidney problems regarding Insulin user and non-user (prevalence more in Insulin non-user) ; Gender, Periodontitis, Feet/Leg cramps, GIT problems regarding daily sunlight exposure (prevalence more in without daily sunlight exposure). Multiple linear regressions confirmed that, diabetic neuropathy related symptoms and complications are less in Insulin user than Insulin non-user (β= .178, 95% CI = .023~.316, p=.023) and sex (p=.000) plays an important role, where female had more diabetic neuropathy related symptoms and complications in than male (β=.341, 95% CI=.190~.477, p =0.000) due to lack of daily sunlight exposure.

[**Key words:** T2DM, Complications, Daily Sunlight-exposure, Diabetic neuropathy]


Introduction

Chapter I: Introduction

Diabetes Mellitus (DM) is a serious chronic disease suffering the Global population for last few centuries. Rising burden of type 2 diabetes is a major concern in healthcare working worldwide. In 2021, approximately 537 million individuals or 10.5% adults were affected by diabetes mellitus of which 90 million are from South-east Asia (IDF, 2021_b). International Diabetes Federation (IDF) told 79% adult diabetic cases are from low- and middle-income countries. IDF also says that, each 1 in 11 adults (90 million) are living with diabetes and is expecting number of adults with diabetes will reach to 643 million by 2030 and 783 million by 2045. According to IDF, for every 1 in 2 adults living with diabetes remain undiagnosed and over 3 in 4 adults with diabetes are living in low- and middle-income countries. In 2021, the total number of 747,000 deaths was caused by diabetes (IDF, 2021_c). In Bangladesh there were 8.4 million adults, living with diabetes in 2019, and it is projected to around 13.7 million by 2045 (IDF, 2019). Previous studies shows that , the prevalence of diabetes among adults has increased substantially from ~5% in 2001 to ~14% in 2017 in Bangladesh *(*Fatema *et al.*,2016; Akter *et al.*,2014; Saquib *et al.*, 2012).

DM is categorized into mainly following three types, Type 1 DM, Type 2 DM and Gestational DM. Type 2 diabetes (formerly called non-insulin-dependent or adult-onset diabetes) results from the body's ineffective use of insulin (ADA, 2018*)*. Type 2 diabetes accounts for 90% of people with DM around the world (Shah *et al.,* 2015*).* Diabetes mellitus cases has been increasing as a chronic case in wider context of South East Asia due to rapid urbanization leading to increasing sedentary life style, dietary excess fat intake and stressful life. Biological factors are also associated with life style that, ultimately lead to 3 fold higher prevalence of Diabetes in South East Asia that comparing to Europe (Mohan , 2004 ; Tillin *et al.,* 2013)

Uncontrolled T2DM can be life threatening if unmanaged. It contributes significantly in costs, mortality and poor quality of life. If it leads to acute conditions like diabetic ketoacidosis (DKA) due to persistent raised blood glucose, it can be life-threatening. In all types of diabetes, seizures or loss of consciousness can occur due to abnormally low blood glucose. T2DM can damage the eyes, heart, blood vessels, nerves and kidneys, and increases the risk of cardiovascular disease and cerebrovascular disease over the time. These damages ultimately resulting in blood flow

reduction, combining with nerve damage (neuropathy) in feet – which increase the risk of foot ulcers, infection and might even lead to limb amputation. An important cause of blindness is Diabetic retinopathy and which results due to long-term accumulated damage to the retinal small blood vessels. T2DM is also one of the leading causes of renal failure (WHO, 2021). Apart from these, diabetes is considered as one of the most important causes of premature death and disability. It is also one of four priority non-communicable diseases (NCDs), on the Prevention and Control of NCDs DM is targeted by world leaders in the 2011 Political Declaration (Morenga *et al.*,2013)

The disease itself is not only causing problems to the patients but also it creates burdens to the family as well. These burdens for both patients and families are due to increase Type 2 DM complications and associated which leads to financial burden. Combinations of all of these ultimately decrease the daily life quality. A study in 2019 in Bangladesh shows that the average annual cost for T2DM patient is US$865 with the medicine cost being the highest contributor followed by the hospitalization cost the average annual cost for patients with hospitalization was 4.2 times higher compared to those without hospitalization. The average annual cost for each person with T2DM in Bangladesh appears to be considerably higher than that reported in previous studies conducted in Bangladesh (US$314) and other South Asian countries such as India (US$525) and Pakistan (US$197) (Afroz *et al.*, 2019_a).

Chattogram is a major coastal city and great financial center situated in the south-eastern part of Bangladesh. It had a population of more than 5,132,751 in 2021 (Statistics times, 2021) which made it the second-largest densely populated city in the country. The city is situated on the banks of the river Karnaphully between the Bay of Bengal and Chattogram Hill Tracts. Modern Chattogram is the second most significant urban center in Bangladesh after Dhaka. By gender, the population was 54.36% male and 45.64% female, and the literacy rate in the city was approximately 72 percent, in 2020. The current practicing religions in Chattogram city include Islam (86%), Hinduism (12%), and others (2%) where the Muslims numbering around at 3.44 million form the overwhelming majority of the city's population and rest being Hindus numbering around at 4.8 lakhs and 2% other religions such as Buddhism and Christianity (Shireen, 2014; Sirajul and Jamal , 2012). Regarding this huge population, in a survey conducted

in Chattogram Medical college Hospital in 2019 shows that women are more prone to diabetes compared to men, which is 61%. In this age distribution, it is observed from above figure 51-60 aged peoples are mainly suffered from the diabetes mellitus. The study also shows 32% are suffered from blood pressure, 33% are suffered from joint pain, 30% are suffered from retinopathy, 15% are suffered from back pain, 7% are suffered from foot pain, 10% are suffered from itching, 7%% are suffered from frequent urination, 20% are suffered from chest pain, 3% are suffered from arthritis and 9% are suffered from allergy (Dey and Islam, 2019). In Bangladesh, besides the above studies no detailed studies have been done regarding Insulin user, daily sunlight exposure and daily exercise and their association with T2DM complications and T2DM associated risk factors. Therefore, the author has decided to conduct a study which will not only be able to find out the prevalence of T2DM complications and T2DM associated risk factors, but also the correlate the probable factors which can reduce the prevalence of T2DM complications.

Considering the above background and the huge impact of T2DM, the present study was conducted with the aim of delivering awareness messages to Type 2 Diabetic patients and general population helping in reducing the prevalence of complications and improve the life style and health cost.

The overall objectives of the present study are :

1. To assess the socio demographic status of the Type 2 DM persons;
2. To assess the biochemical markers related to diabetic complications;
3. To assess complications and factors associated with T2DM;
4. To assess the type of anti-diabetic medications taken by study subjects.

Review of Literature

Chapter-II: Review of Literature

2.1 History of Diabetes

The term diabetes mellitus which is shortly named diabetes is derived from the Greek word diabetes which means siphon - to pass through and the Latin word mellitus meaning honeyed or sweet. This is because in diabetes excess sugar is found in blood as well as the urine. It was known in the 17^{th} century as "the pissing evil"

It was probably coined by Apollonius of Memphis around 250 BC. Diabetes mellitus was first recorded in English, in the form diabetes, in a medical text written around 1425. In 1675, Thomas Willis added the word "'mellitus'" with the word diabetes due to sweet taste of the urine. This sweet taste also noticed in urine by the ancient Greeks, Chinese, Egyptians, Indians, and Persians as is evident from their literature (Anannya$_a$, 2019).

2.2 Concept of Diabetes

By definition, Diabetes Mellitus (DM) is a chronic condition, a disorder of metabolism characterized by increased concentration of sugar in blood (hyperglycemia) caused by either i) insufficient insulin secretion or ii) insulin action resistance or iii) a combination of both i) and ii). This chronic hyperglycemia results in long-term damage of various organs, mainly, the eyes, blood vessels, kidneys, nerves and the heart (Dolley, 2016). IDF says currently 537 million adult individuals aged 20–79 years are affected by type 2 diabetes corresponding to 10.5%of the world's population (IDF, 2021$_b$).

2.3 Types of Diabetes Mellitus:

There are mainly three types of diabetes:-

- Type-1 diabetes (T1DM)
- Type-2 diabetes (T2DM)
- Gestational diabetes
- Specific types of diabetes due to other causes (ADA, 2018)

2.3.1 Type-1 Diabetes:

Type 1 diabetes is caused due to an autoimmune reaction where the body's immune system attacks the cells (β cell of pancreas) which produce insulin. As a result, the pancreas produces very little or no insulin. Though the exact causes are not known yet, but they are linked to a combination of genetic and environmental conditions. Type 1 diabetes can affect people at any age, but it usually develops in children or young adults. People with type 1 diabetes need to take daily insulin injections to control their blood glucose levels. If people with type 1 diabetes do not have access to insulin, the ultimate end result will be death.

The most common symptoms of type 1 diabetes include:

- Abnormal thirst and dry mouth
- Sudden weight loss
- Frequent urination
- Lack of energy, tiredness
- Constant hunger
- Blurred vision

2.3.2 Type-2 Diabetes Mellitus (T2DM):

It is generally characterized by insulin resistance, in where the body does not fully respond to insulin. As because insulin cannot work properly, the blood glucose levels keep rising, resulting in releasing more insulin. In some individuals with type 2 diabetes this phenomenon can eventually exhaust the pancreas, ultimately resulting in the pancreas to produce less and less insulin, leading to even higher blood sugar levels (hyperglycemia). Type 2 DM is usually occur in older adults, also surprisingly increasing observed in younger adults due to rising number of obesity, physical inactivity and unhealthy diet.

The symptoms of T2DM similar to those of T1DM and include:

- Excessive thirst and dry mouth
- Frequent urination
- Lack of energy, tiredness
- Slow healing wounds
- Blurred vision
- Recurrent infections in the skin
- Tingling or numbness in hands and feet.

2.3.3 Gestational Diabetes Mellitus:

Gestational diabetes mellitus (GDM) is a severe and neglected issue to maternal and child health. Many women with GDM face pregnancy-related complications due to uncontrolled blood sugar level or due to GDM itself. Approximately half of women with a history of GDM go on to develop type 2 diabetes within five to ten years after delivery (Dianna *et al.*, 2021).

2.3.4 Specific types of diabetes due to other causes:

Monogenic diabetes syndromes [such as neonatal diabetes and maturity-onset diabetes of the young (MODY), diseases of the exocrine pancreas (such as cystic fibrosis and pancreatitis), and drug or chemical-induced diabetes (such as with glucocorticoid use, in the treatment of HIV/AIDS, or after organ transplantation] are in the category of this type of diabetes. (ADA, 2018)

2.4 Diagnosis of Diabetes Mellitus:

Diabetes mellitus can be diagnosed in multiple ways. Each way usually needs to be repeated again on a second time to confirm diabetes.

2.4.1 HbA1C: The Glycosylated Hemoglobin in short HbA1C or simply A1C refers to the average blood sugar of last two to three months. Diabetes is diagnosed if the A1C of greater than or equal to 6.5% (The hemoglobin A1c test tells the average level of blood sugar over the past 2 to 3 months. It is shown in % .

Table 1: Diagnosis of DM regarding HbA1C

Result	HbA1C
Normal	less than 5.7%
Pre-diabetes	5.7% to 6.4%
Diabetes	6.5% or higher

2.4.2 Fasting Plasma Glucose (FPG): The test checks the fasting blood sugar levels. Fasting means having no food or drink (except water) for at least 8 hours before the test. This test is usually done as the first task in the morning, before breakfast. Diabetes is confirmed if fasting blood sugar is greater than or equal to 126 mg/dl.

Table 2: Diagnosis of DM regarding Fasting Plasma glucose

Result	Fasting Plasma Glucose (FPG)
Normal	less than 100 mg/dl
Pre-diabetes	100 mg/dl to 125 mg/dl
Diabetes	126 mg/dl or higher

2.4.3 Oral Glucose Tolerance Test (OGTT): The OGTT is a test that checks the blood sugar levels before and two hours after drinking a special sweet drink usually a drink of 75gm oral glucose solution. It tells us how our body processes sugar. Diabetes is diagnosed at 2 hour blood sugar of greater than or equal to 200 mg/dl.

Table 3: Diagnosis of DM regarding Oral Tolerance Test (OGTT)

Result	Oral Glucose Tolerance Test (OGTT)
Normal	less than 140 mg/dl
Pre-diabetes	140 mg/dl to 199 mg/dl
Diabetes	200 mg/dl or higher

2.4.4 Random (also called Casual) Plasma Glucose Test: This test is a blood check at any time of the day if anyone has severe diabetes symptoms. Diabetes is diagnosed at blood sugar of greater than or equal to 200 mg/dl (ADA, 2018)

2.5 Risk factors of Diabetes Mellitus:

The causes of diabetes are not known. The following risk factors may increase your chance of getting diabetes:

2.5.1 Non-modifiable risk factors for Type 2 diabetes: Risk factors that increase our risk for developing pre-diabetes and Type 2 diabetes that can't be changed are:

- Family history of T2DM: The risks of diabetes are increased if it is inherited from parents or close biological relatives. If a person has a blood relative with diabetes, the risk for developing it is significantly increased.

- Race or ethnic background: The African-American, Asian-American, Latino/Hispanic-American and Native American or of Pacific-Islander descent will have a greater chance of developing diabetes.
- Age: Persons are in risk for pre-diabetes and Type 2 diabetes with increasing the age. Generally Type 2 diabetes mellitus used to occur in middle-aged adults, most frequently after age 40. But health care professionals are currently diagnosing more children and adolescents with T2DM.
- Gestational diabetes: If any female developed diabetes during pregnancy, she is at increased risk of developing T2DM again in her later life.

2.5.2 Modifiable risk factors for Type 2 Diabetes: We can and should do something about our modifiable risk factors. We can reduce our risk for diabetes or delay its development by making healthy changes:

- Weight: Overweight or obese increases the risk of developing diabetes. Losing 5% to 10% of body weight with addition of doing regular physical activity—can significantly reduce risk of developing diabetes. Risk decreases even more as the person loses more weight for height (Editorial, 2021).
- Physical activity: Physical inactivity is one of the most important modifiable risk factor for pre-diabetes and Type 2 diabetes. Daily physical activity helps lower insulin resistance which means body can use its own insulin more effectively. A brisk walk of 30-minute at least five days a week has been shown to significantly reduce the risk of diabetes and heart disease eventually. For overall cardiovascular health, at least 150 minutes per week of moderate-intensity aerobic physical activity, or 75 minutes per week of vigorous-intensity aerobic physical activity (or a combination of the two) and muscle-strengthening at least two days per week should be done (Editorial, 2021).
- Blood pressure: Uncontrolled high blood pressure has been linked to complications from diabetes. People with diabetes with high blood pressure should maintain a blood pressure of less than 130/80 mm Hg. The normal blood pressure for a non-diabetic person should be below 120/80 mm Hg (Editorial, 2021).

- Cholesterol (lipid) levels: Diabetes mellitus is associated with atherosclerosis (hardening of the arteries) and blood vessel disease. Low high density lipoprotein (HDL) and/or high triglycerides can increase the risk for Type 2 diabetes and cardiovascular disease.
- Smoking: It is considered as one of the most important modifiable risk factor for Diabetes mellitus.
- Diet: Unhealthy and uncontrolled diet is one of the most important modifiable risk factors for pre-diabetes and Type 2 diabetes.
- Alcohol: Heavy alcohol consume can cause inflammation in the pancreas and limits its ability to produce enough insulin for body. It can also cause liver damage and it adds more sugar and starch to our diet, that must has to be used or will be stored as fat.
- Stress and well-being: Managing the stress in our lives is an important part of healthy living.
- Sleep: An adult should have seven to nine hours of sleep a night. Sleep improves mood, memory and reasoning. (Editorial, 2021)

Though the relationship may vary in different population, the higher waist circumference and higher body mass index (BMI) are associated with increased risk of T2DM, (Vazquez *et al.,* 2007). South-East Asian people tend to develop diabetes at a low BMI than people of European origin (Ramachandranet *al.,* 2010). Active smoking increases the risk of T2DM (Willi *et al.,*2007). And the risk remains elevated for about around 10 years after of smoking cessation, which decreases quickly for lighter smokers (Luo *et al.,* 2013).

2.6 Pathophysiology of Diabetes Mellitus:

Glucose is the primary source of energy for the human body. Absorbed from the intestine it is metabolized by:

- energy production (by conversion to water and carbon dioxide)
- conversion to amino acids and proteins or keto-acids
- storage as glycogen

Metabolism of glucose is regulated by complex orchestration of hormonal activities. Daily sugars which are being intake are broken down into various carbohydrates. The most important is glucose, metabolized in nearly all body cells. Glucose enters the cell by facilitated diffusion

(glucose transport proteins). This facilitated transport is stimulated very rapidly and effectively by an insulin signal (glucose transport into muscle and adipose cells is increased up to twenty fold). After glucose is transported into the cytoplasm, insulin then directs the disposition of it - conversion of glucose to glycogen, to pyruvate and lactate, and to fatty acids. Diabetes was initially diagnosed by the use of oral glucose tolerance test (OGTT) and the criteria were changed many times by World Health Organization and American Diabetic Association. The main pathophysiology of three types of Diabetes Mellitus are given below

2.6.1 Type 1 diabetes:

The terms insulin-dependent diabetes or juvenile-onset diabetes previously encompassed this type of diabetes. Type 1 diabetes results from an autoimmune destruction of the ß-cells of the pancreas. There are several markers of this autoimmune destruction, detectable in body fluids and tissues:

- Islet cell autoantibodies (ICAs)
- Autoantibodies to insulin (IAAs)
- Autoantibodies to glutamic acid decarboxylase (GAD65)
- Autoantibodies to the tyrosine phosphatases IA-2 and IA-2ß.

Despite increased knowledge, we are still far from understanding the etiology of T1DM. There is no doubt that genetic factors are strongly implicated as several genetic factors have been identified. On the other hand the concordance rate in twin studies is under 50% supporting the very important role of environmental factors, amongst which viral infections have to be counted. Type 1 diabetes mellitus results from a cellular-mediated autoimmune destruction of the insulin-secreting cells of pancreatic ß-cells. The autoimmune process begins many years before clinical detection and presentation. The destruction must be very heavy as 10-20% of the volume of ß-cells is sufficient to cover clinical symptoms. The rate of ß-cell destruction is quite variable, being rapid in some individuals (mainly infants and children) and usually slow in adults (Palicka, 2002).

2.6.2. Type 2 diabetes mellitus:

Type 2 diabetes mellitus was formerly known as non-insulin-dependent diabetes mellitus (NIDDM), type II, or adult-onset diabetes. It is much more common that Type 1 Diabetes and comprises approximately 90% of all individuals with diabetes. The patients are usually older at the onset of disease, mostly present only minimal symptoms. Insulin concentrations are mostly increased but they can be normal or decreased. Obesity is quite common and weight reduction ameliorates the hyperglycemia. The disease usually develops after 40 years of age. Oral hypoglycemic drugs and dietary manipulation represent the biggest role in therapy; insulin is sometimes required to correct hyperglycemia. The groups of disorders, of which two are most common, represent the new knowledge type 2 diabetes mellitus (Palicka, 2002).

The first one is a decreased ability of insulin to act on peripheral tissues. Usually we call it "insulin resistance". Insulin resistance is defined as a decreased biological response to normal concentrations of circulating insulin and represents the primary underlying pathological process. The second is the dysfunction of pancreatic ß-cells, represented by the inability to produce sufficient amount of insulin to overcome insulin resistance in the peripheral tissues. Later on the insulin production can be insufficient to compensate the insulin resistance due to ß-cells dysfunction. The common result is the relative deficiency of insulin. Long discussion was held about the primary reason - insulin resistance or derangement of insulin production. Data support the concept that insulin resistance is the primary defect, preceding the derangement of insulin secretion. Insulin resistance usually precedes the clinical signs by as much as 20 years. The basis of insulin resistance and insulin secretion defect results from a combination of environmental and genetic factors (Palicka, 2002).

2.6.3. Gestational diabetes mellitus:

Gestational diabetes mellitus is usually asymptomatic and not life threatening to the mother. The condition is associated with an increased incidence of neonatal morbidity, neonatal hypoglycemia, macrosomia and jaundice. Even normal pregnancies are associated with increasing insulin resistance, mostly in the second and third trimesters. Euglycaemia is maintained by increasing insulin secretion. In those women who are not able to increase the secretion of insulin, gestational diabetes develops.

The pathophysiology of gestational diabetes mellitus is not well known and includes family history of diabetes mellitus, obesity, complications in previous pregnancy (ies) and advanced maternal age. It is essential to detect pre-existing diabetes mellitus which has a much worse prognosis for the fetus (Palicka, 2002).

2.7 Complications of Type 2 Diabetes Mellitus:

1. Microvascular complications:
    - Diabetic Retinopathy: Leading to cataract and blindness
    - Diabetic Nephropathy: Renal failure
    - Diabetic Neuropathy: Peripheral neuropathy, Sensory polyneuropathy causing burning, sensory loss, motor weakness, autonomic neuropathy, postural hypotension, GI problems (gastro paresis; altered bowel habit), periodontitis, sexual dysfunction, psychological problems, foot disease ulceration, arthropathy
2. Macrovascular complications:
    - Coronary circulation: Myocardial ischaemia/infarction
    - Cerebral circulation: Transient ischemic attack (TIA), stroke
    - Peripheral circulation: Claudication (It is the pain in thigh, calf, or buttocks that happens during walking. This is a symptom of peripheral artery disease (PAD) and it occurs when narrowed or blocked artery reduces the blood flow to the legs), ischaemia
3. Important associated factors:
    - Hypertension
    - Dyslipidemia

2.7.1 Microvascular complications of Diabetes Mellitus:

2.7.1.1 **Diabetic retinopathy:**

Diabetic retinopathy (DR) is a common cause of blindness in adults. Hyperglycemia increases retinal blood flow and metabolism, and has direct effects on retinal endothelial cells, resulting in impaired vascular auto regulation. This leads to chronic retinal hypoxia, which stimulates production of growth factors and causes new vessel formation and increased vascular permeability (Innes, 2020).

Clinical features of Diabetic Retinopathy (DR): It is a progressive condition, comprising non-proliferative ('background') and proliferative stages. The earliest signs of non-proliferative DR are micro-aneurysms and retinal hemorrhages, sometimes inaccurately called 'dot' and 'blot' hemorrhages. As DR progresses, cotton wool spots, venous beading and intra-retinal micro-vascular abnormalities appear, this is referred to as pre-proliferative DR. Progression to proliferative DR is characterized by growth of new blood vessels on the retina or optic disc. These vessels are abnormal and often bleed, causing vitreous hemorrhage, subsequent fibrosis and scarring, and finally tractional retinal detachment (Innes, 2020).

In addition, patients may also develop clinically significant macular edema. This can occur at any stage of DR and is the most common cause of loss of vision in diabetes. Proliferative retinopathy and severe ocular ischemia may stimulate new vessels to grow on the anterior surface of the iris: 'rubeosisiridis'. These vessels may obstruct the drainage angle of the eye, causing secondary glaucoma. Loss of visual acuity: Micro-aneurysms, abnormalities of the veins, and small hemorrhages and exudates situated in the periphery will not interfere with vision. However, if these changes appear near the macula, and in particular if they are accompanied by loss of visual acuity, Clinically Significant Macular Oedema (CSMO) should be suspected (Innes, 2020).

Macular edema can cause impaired visual acuity, even if only mild peripheral non-proliferative retinopathy is present. Macular edema can only be confirmed or excluded on slit lamp retinal bio microscopy. Sudden visual loss occurs with vitreous hemorrhage or retinal detachment. In pre-proliferative and proliferative retinopathy, with or without visual impairment, prompt laser treatment is important to reduce the risk of hemorrhage, fibrosis/gliosis and irreversible visual impairment. Cataract occurs prematurely in people with diabetes due to the metabolic problem to the lens (Innes, 2020).

2.7.1.2 Diabetic nephropathy:

T2DM may present with albuminuria at the time the diabetes is detected. Due to T2DM structural and functional changes occur in the kidney which results in proteinuria, hypertension, and progressive reduction of kidney function. This is the hallmark of diabetic nephropathy. Persistent rise of blood glucose leads to the production of reactive oxygen molecules and activation of multiple pathways, including protein kinase C, polyol, hexosamine, and advanced glycation end (AGE) products. Marked inflammation manifested by increasing cytokines and chemokines, causing inflammation, fibrosis and increased vascular permeability (Ron and Jialal, 2021). An albuminuria result due to podocytopathy (Any disease that affects the podocytes of the glomerulus of the kidney, usually resulting in proteinuria). The systemic and intraglomerular hypertension results proteinuria. Proteinuria leads to chronic tubular injury. Criteria for diagnosis include:

- High Blood pressure
- Decreasing glomerular filtration rate (GFR)
- Persistent albuminuria (greater than 300 mg/d) on at least two visits 3-6 months apart. (Ron and Jialal, 2021)

The global rise of T2DM causes the Diabetic Nephropathy as the most frequent cause of end-stage renal disease (ESRD). In 2009–2011, it was found that, diabetes mellitus was the primary cause of ESRD in about 60% of patients in Mexico, Malaysia, and Singapore. Countries where ESRD incidence of 40%–50% include Korea, Israel, Taiwan Hong Kong, , Japan, Philippines, New Zealand, and the US. ESRD incidence due to diabetes mellitus rise in the older age people. In 2011, the ESRD incident rates due to diabetes mellitus in the US were 44, 266, and 584 per million for the age groups 20–44, 45–64, and 65–74 years, respectively (Amit and Ramakant, 2021). A similar finding also noted in the Australian Diabetic study of 11,247 diabetic Australians (Andy, 2014).

Urine analysis is done to measure urea, creatinine, and protein (Ron and Jialal, 2021). Risk factors for developing nephropathy include:

- Poor glycemic control duration of diabetes
- Other microvascular complications

- Ethnicity: Asian, Pima Indians
- Hypertension
- Family history of nephropathy or hypertension.

Pathologically, thickening of the glomerular basement membrane is followed by nodular deposits (Kimmelstiel–Wilson nodules). As glomerulosclerosis worsens, heavy proteinuria develops, sometimes in the nephrotic range, and renal function progressively deteriorates.

2.7.1.3 Diabetic neuropathy:

This complication affects 50–90% of patients. It is usually symptomless in the majority and involves motor, sensory and autonomic nerves. Prevalence is related to the duration of T2DM and the amount of metabolic control.

Clinical features of Diabetic neuropathy:

- Symmetrical sensory polyneuropathy: This is commonly asymptomatic. The most common signs are diminished perception of vibration distally, 'glove-and-stocking' impairment of all sensory modalities, and loss of tendon reflexes in the legs. Symptoms may include par-aesthesia in the feet or hands, pain on the anterior aspect of the legs (worse at night), burning sensations in the soles of the feet, hyperesthesia and a wide-based gait. Toes may be clawed with wasting of the interosseous muscles. A diffuse small-fiber neuropathy causes altered pain and temperature sensation and is associated with symptomatic autonomic neuropathy; characteristic features include foot ulcers and Charcot neuroarthropathy, asymmetrical motor diabetic neuropathy (diabetic amyotrophy). This presents as severe, progressive weakness and wasting of the proximal muscles of the legs (occasionally arms), accompanied by severe pain, hyperesthesia and paraesthesia. There may also be marked loss of weight ('neuropathic cachexia') and absent tendon reflexes; the CSF protein is often raised. This condition is thought to involve acute infarction of the lumbosacral plexus. Although recovery usually occurs within 12 months, some deficits become permanent. Management is mainly supportive (Innes, 2020).
- Mono neuropathy: Either motor or sensory function can be affected within a single peripheral or cranial nerve. Unlike other neuropathies, mono neuropathies are severe and of rapid onset. The patient usually recovers. Most commonly affected are the 3rd and 6th cranial nerves (causing diplopia), and femoral and sciatic nerves. Multiple nerves are affected in mononeuritis multiplex.

Nerve compressions (palsies) commonly affect the median nerve and lateral popliteal nerve (foot drop) (Innes, 2020).

- Autonomic neuropathy: This is less clearly related to poor metabolic control, and improved control rarely improves symptoms. Within 10 years of developing autonomic neuropathy, 30–50% of patients are dead. Postural hypotension indicates a poor prognosis (Innes, 2020).
- Sexual dysfunction: This affects 30% of diabetic males and is often multifactorial. Psychological problems, depression, alcohol and drug therapy may contribute (Innes, 2020).
- The diabetic foot tissue necrosis in the feet is a common reason for hospital admission in diabetic patients. Foot ulceration occurs as a result of often trivial trauma in the presence of neuropathy (peripheral and autonomic) and/or peripheral vascular disease; infection occurs as a secondary phenomenon. Most ulcers are neuropathic or neuroischaemic in type. They usually develop at the site of a plaque of callus skin, beneath which tissue necrosis occurs, eventually breaking through to the surface. Charcot neuroarthropathy (A syndrome in patients who have peripheral neuropathy, or loss of sensation, in the foot and ankle), with destructive inflammation of neuropathic joints, is usually caused by diabetes (Innes, 2020).
- Postural or orthostatic hypotension: Postural or orthostatic hypotension which is a core feature of autonomic failure is defined as a fall in the blood pressure of 20/10 mmHg on standing for three minutes. It is commonly encountered in the subjects where common symptoms are lightheadedness, discomfort in the head (typically occipital), shoulders, neck, sometimes the chest and mining of vision. It is the most annoying symptom, often complained by the patients suffering from diabetic neuropathy (Metzler *et al.,* 2013). Diabetes can also damage the nerves supplying in the blood vessels, which in turn can lead to a drop in blood pressure upon standing up or any other sudden movements where your blood vessels may find it hard to adjust (Innes, 2020).
- Gastrointestinal (GI) problems: Gastrointestinal (GI) disorders are common among all people, including those affected by diabetes. At some point in any patient's life, the chances that he or she will develop a GI tract problem, be it peptic ulcer disease, gallstones, irritable bowel syndrome, food poisoning, or some other malady, are extremely high (James and Edelman, 2000). As many as 75% of patients visiting diabetes clinics are report significant GI symptoms. The entire GI tract can be affected by diabetes from the oral cavity and esophagus to the large bowel and anorectal region. Thus, the symptom complex that may be experienced can vary

widely. Common complaints may include dysphagia, early satiety, reflux, constipation, abdominal pain, nausea, vomiting, and diarrhea. Many patients go undiagnosed and under-treated because the GI tract has not been traditionally associated with diabetes and its complications. Both acute and chronic hyperglycemia can lead to specific GI complications. Diabetes is a systemic disease that may affect many organ systems, and the GI tract is no exception. As with other complications of diabetes, the duration of the disorder and poor glycemic control seem to be associated with more severe GI problems. Patients with a history of retinopathy, nephropathy, or neuropathy should be presumed to have GI abnormalities until proven otherwise, and this is best determined by asking a few simple questions. Many GI complications of diabetes seem to be related to dysfunction of the neurons supplying the enteric nervous system. Just as the nerves in the feet may be affected in peripheral neuropathy, involvement of the intestinal nerves may lead to enteric neuropathy. This is a type of autonomic or "involuntary" neuropathy and may lead to abnormalities in intestinal motility, sensation, secretion, and absorption. Different nerve fibers can either stimulate or inhibit intestinal motility and function, and damage to these nerves can lead to a slowing or acceleration of intestinal function, giving rise to a variable symptom complex.

- Loss of Cognitive Function: There is a link between cognitive deficit and diabetes. Compared to those without diabetes, (Cukierman, 2005). "Having diabetes, especially when on insulin, increases the risk of falls in older people (Yang *et al.,* 2016).

2.7.2 Macro vascular Complications of Diabetes Mellitus: Following are the microvascular complications.

2.7.2.1 **Ischemic Heart Disease (IHD):**

Ischemic Heart Disease is a disorder of the heart and blood vessels. Diabetes increases the risk that an individual will develop Ischemic Heart Disease (IHD). IHD is the primary cause of death in people with either type 1 or type 2 diabetes mellitus. In fact, IHD accounts for the greatest component of health care expenditures in people with diabetes (Paterson *et al.,* 2107). IHD has been associated with diabetes in numerous studies beginning with the Framingham study (Kannel and McGee, 1979). More recent studies have shown that the risk of myocardial infarction (MI) in people with diabetes is equivalent to the risk in non-diabetic patients with a history of previous MI (Myocardial Infarction) (Haffner *et al.,*1998). These discoveries have led

to new recommendations by the American Diabetic Association (ADA) and American Heart Association that diabetes be considered a coronary artery disease risk equivalent rather than a risk factor (Buse *et al.,* 2007).

Type 2 diabetes typically occurs in the setting of the metabolic syndrome, which also includes abdominal obesity, hypertension, hyperlipidemia, and increased coagulability. These other factors can also act to promote IHD. Even in this setting of multiple risk factors, type 2 diabetes acts as an independent risk factor for the development of ischemic disease, stroke, and death (Almdal *et al.,* 2004). Among people with type 2 diabetes, women may be at higher risk for coronary artery disease than men. The presence of microvascular disease is also a predictor of coronary heart events (Avogaro *et al.,*2007). Patients with type 1 diabetes also bear a disproportionate burden of coronary heart disease. Studies of have shown that these patients have a higher mortality from ischemic heart disease at all ages compared to the general population. In individuals > 40 years of age, women experience a higher mortality from ischemic heart disease than men (Laing *et al.,* 2003).

In addition to atheroma formation, there is strong evidence of increased platelet adhesion and hypercoagulability in type 2 diabetes. Impaired nitric oxide generation and increased free radical formation in platelets, as well as altered calcium regulation, may promote platelet aggregation. Elevated levels of plasminogen activator inhibitor type 1 may also impair fibrinolysis in patients with diabetes. The combination of increased coagulability and impaired fibrinolysis likely further increases the risk of vascular occlusion and cardiovascular events in type 2 diabetes *(*Joshua *et al.,* 2002).

A patient without any history of myocardial infarction (MI), the 7-year risk of MI is 20.2% and 3.5% for diabetes mellitus patients versus non-diabetic patients, respectively. Same as, in patients with history of MI, the 7-year risk of MI is 45.0% and 18.8% for, diabetes mellitus patients versus non-diabetic patients respectively *(*Haffner *et al.,* 1998). This 7-year risk of developing MI comparing suggests that diabetes mellitus significantly contributes in developing MI and can possibly be considered as an IHD risk equivalent.

2.7.2.2 Cerebrovascular Disease (CVD):

Diabetes is also a strong independent predictor of risk of stroke and cerebrovascular disease (CVD) , as in coronary artery disease (Lehto *et al.,* 1996). Patients with Type 2 diabetes have a much higher risk of stroke, with an increased risk of 150-400%. Risk of stroke-related dementia and recurrence, as well as stroke-related mortality, is elevated in patients with diabetes (Joshua *et al.,* 2002). Observational studies have shown that the cerebrovascular mortality rate is elevated at all ages in patients with type 1 diabetes (Laing *et al.,* 2003_b).

2.7.2.3 The overall impact of IHD and CVD due to T2DM:

The increased risk of IHD has led to more aggressive treatment of these conditions to achieve primary or secondary prevention of coronary heart disease before it occurs. Studies in type 1 diabetes have shown that intensive diabetes control is associated with a lower resting heart rate and that patients with higher degrees of hyperglycemia tend to have a higher heart rate, which is associated with higher risk of IHD (Paterson *et al.,* 2107). Even more conclusively, the Diabetes Control and Complications Trial/Epidemiology of Diabetes Interventions and Complications Study demonstrated that during 17 years of prospective analysis, intensive treatment of type 1 diabetes, including lower A1C, is associated with a 42% risk reduction in all cardiovascular events and a 57% reduction in the risk of nonfatal MI, stroke, or death from IHD (Nathan *et al*., 2005).

There has not been a large, long-term, controlled study showing decreases in macro vascular disease event rates from improved glycemic control in type 2 diabetes. Modification of other elements of the metabolic syndrome, however, has been shown to very significantly decrease the risk of cardiovascular events in numerous studies. Blood pressure lowering in patients with type 2 diabetes has been associated with decreased cardiovascular events and mortality. The United Kingdom Prospective Diabetes Study was among the first and most prominent study demonstrating a reduction in macro vascular disease with treatment of hypertension in type 2 diabetes (UKPDS,1998_a).

Blockade of the renin-angiotensin system using either an Angiotensin Converting Enzyme inhibitor or an Angiotensin Receptor Blocker reduced cardiovascular endpoints more than other

antihypertensive agents. It should be noted that use of ACE inhibitors and ARBs also may help slow progression of diabetic microvascular kidney disease. Multiple drug therapy, however, is generally required to control hypertension in patients with type 2 Diabetes Mellitus (Lindholm *et al.,* 2002). The central pathological mechanism in macrovascular disease is the process of atherosclerosis, which leads to narrowing of arterial walls throughout the body. Atherosclerosis is thought to result from chronic inflammation and injury to the arterial wall in the peripheral or coronary vascular system. In response to endothelial injury and inflammation, oxidized lipids from Low Density Lipoprotein particles accumulate in the endothelial wall of arteries. Angiotensin II may promote the oxidation of such particles. Monocytes then infiltrate the arterial wall and differentiate into macrophages, which accumulate oxidized lipids to form foam cells. Once formed, foam cells stimulate macrophage proliferation and attraction of T-lymphocytes. T-lymphocytes, in turn, induce smooth muscle proliferation in the arterial walls and collagen accumulation. The net result of the process is the formation of a lipid-rich atherosclerotic lesion with a fibrous cap. Rupture of this lesion leads to acute vascular infarction (Boyle, 2007)

A study in 2018 regarding systematic literature review of scientific evidence from worldwide showed that, IHD affected 32.2% overall (53 studies, N = 4,289,140); 29.1% cases had atherosclerosis (4 studies, N = 1153), 21.2% cases had coronary heart disease (42 articles, N = 3,833,200), 14.9% cases had heart failure (14 studies, N = 601,154), 14.6% had angina (4 studies, N = 354,743), 10.0% had myocardial infarction (13 studies, N = 3,518,833) and 7.6% had stroke (39 studies, N = 3,901,505). Globally, IHD affects approximately overall 32.2% of all T2DM persons. It is a major cause of mortality among T2DM people and IHD was the cause of death for 9.9% of T2DM cases (representing 50.3% of all deaths) (Einarson *et al.,* 2018*)*

2.8 Mechanism of Diabetic complications:

The mechanism of diabetes complications, both Microvascular and Macrovascular are showed below. These complications are due to chronic elevation of blood glucose levels leading to damage of blood vessels (angiopathy; Figure1). In diabetes Mellitus, the complications are grouped into "Microvascular disease" (caused by damage to small blood vessels) and "Macrovascular disease" (caused by damage to the arteries).

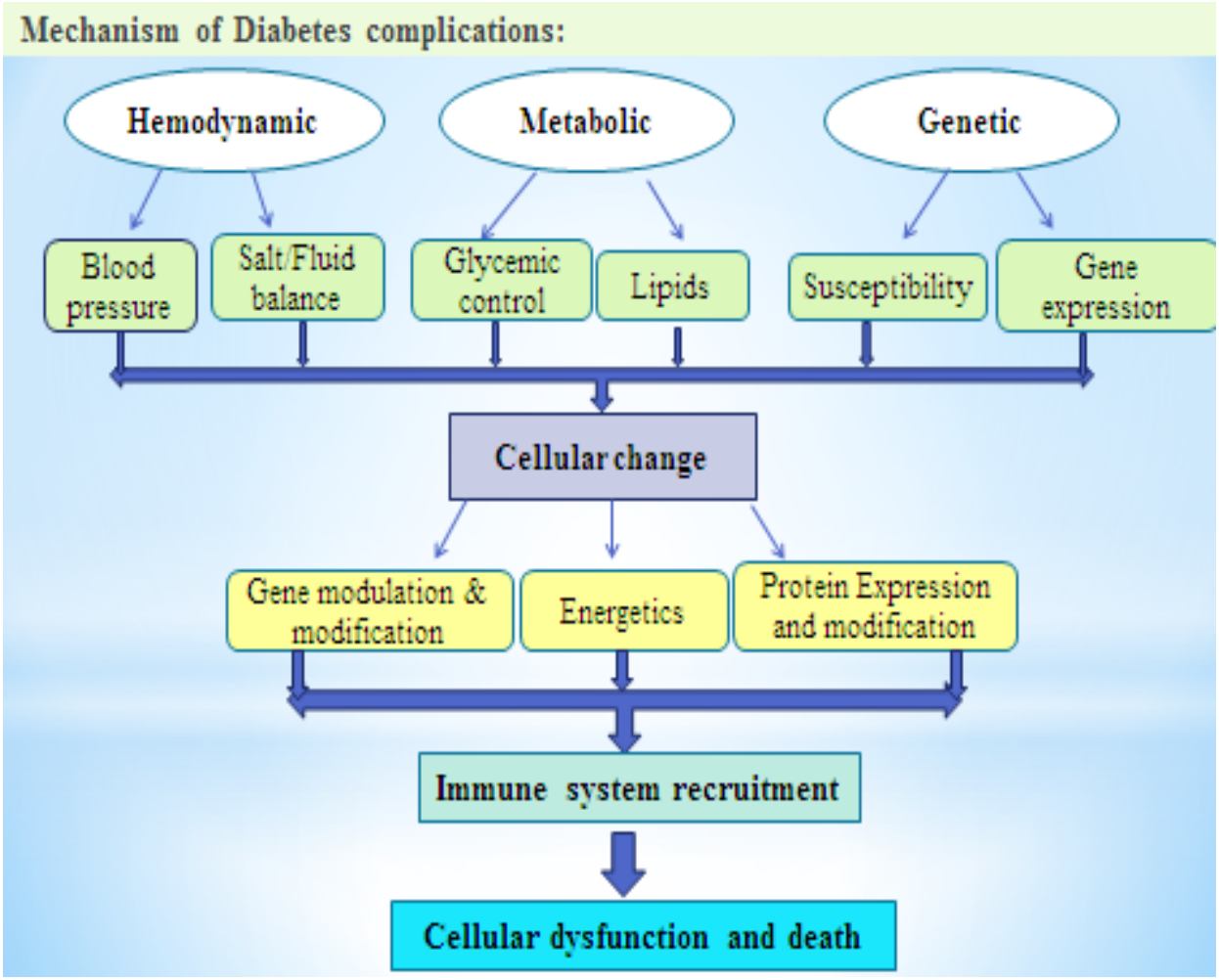


Figure 1: Schematic overview of major areas contributing to Diabetic complications (Forbes and Cooper, 2013. pp 138).

2.8.1 Diabetic Nephropathy:

Diabetic Nephropathy is clinically characterized by the overt proteinuria with a decline in glomerular filtration rate, progresses over a long period of time, often over 10–20 years. If left untreated, the result might be fatal (Mogensen *et al.*, 1983). Importantly, Diabetic Nephropathy

is a major risk factor for the developing macrovascular complications such as CVD and strokes (Matsushita *et al*., 2010). Hypertension (BMJ, 1998) and poor glycemic control (UKPDS, 1998_b) frequently precede overt diabetic nephropathy, although some patients develop nephropathy in spite of good glycemic control (DCCTRG, 1993) and normal blood pressure. Once nephropathy is established, blood pressure is often seen to rise, but in short term, there could be improvements in glycemic control as a result of reduced renal insulin clearance by the kidney (Amico and Klein, 1981). High glucose concentrations induce specific cellular effects have been reported to occur early in diabetes and characterized by glomerular hyper filtration (O'Bryan and Hostetter, 1997). Recent data suggesting that diabetic person who maintains normal glomerular filtration or hyper filtration are protected against the progression to end-stage kidney disease (Groop *et al.,* 2009). Changes in the metabolic pathway, vasoactive factors release, signal transduction alterations (Figure 1) are considered as a result to these hemodynamic changes. Significant hypertrophy occurs to early diabetic kidney. Enlargement of the kidney is often observed at the diagnosis time of diabetes (Rasch and Nőrgaard, 1983). Greater than 90% of the cortical mass is constitute by the proximal tubule in the kidney, accounts for the greatest change in growth in diabetes (Dorup *et al.*,1992; Seyer *et al.*,1980). As the tubule grows it increases the glomerular filtration rate (GFR) (Vallon *et al.,* 2003). Ultimately, extracellular matrix deposition in the tubular component of the kidney (tubulointerstitial fibrosis) is the major determinant of the progression of renal disease in diabetes (Mauer *et al.,* 1984).

2.8.2 Diabetic Retinopathy (DR):

DR is the leading cause of blindness among adults aged 20–74 years. The spectrum of continuous changes includes vascular permeability changes, micro aneurysms of capillary, capillary degeneration, neovascularization. Clinically, DR is classified into non-proliferative and proliferative stages. In the early stages, hyperglycemia leads to intramural pericyte death and basement membrane thickening, ultimately cause changes in blood vessels integrity within the retina, altering the vascular permeability and blood-retinal barrier (Frank, 2004). Most people do not notice any visual impairment in the initial stage of non-proliferative diabetic retinopathy (NPDR).Retinal capillaries degeneration or occlusion are strongly associated with worsening prognosis (Bresnick *et al.,* 1976), it is most likely the result of ischemia . Ultimately progress the disease into the proliferative phase where accumulation of fluid with in the retina and

neovascularization (macular edema), contribute to visual impairment. (Frank,2004). Diabetic retinopathy needs many years to developed (Hirai *et al.,* 2011) and most having type 2 diabetes (Kempen *et al.,* 2004), after 20 show some retinal lesions (Klein *et al.,* 2008)

2.8.3 Diabetic Neuropathy:

More than 50% of all diabetes individuals will eventually develop neuropathy (Abbott *et al.,* 2011), 15% with one or more, lower extremity amputations lifetime risk of estimated in some populations. It is a syndrome which combination of both the autonomic and somatic divisions of the peripheral nervous system. Damage to the spinal cord (Selvarajah *et al.,* 2006) and the higher central nervous system (Wessels *et al.,* 2006) also can occur. Neuropathy is a major factor contributing in the wound healing impairment, erectile dysfunction, and cardiovascular dysfunction in diabetes. Patients, with pain evident in 40–50% of those with diabetic neuropathy show hyperalgesia, paraesthesia, and allodynia (Obrosova , 2009). Recent evidence suggests that diabetic neuropathy targets sensory and autonomic neurons over motor neurons selectively, with little vascular involvement. In particular, the loss of epidermal (Pittenger *et al.,* 2004; Shun *et al.,* 2004) and corneal innervations (Malik *et al.,* 2003) has been noted. The syndrome is commonly termed as "glove and stocking" distribution including numbness, dysesthesia (pins and needles), nighttime pain and sensory loss. Spatial awareness of limb location is also affected early in the disease progression. Loss of sensation in response to injury ultimately leads to develop foot and leg ulcers, may ultimately resulting in amputation. Some diabetic person may develop Charcot joint. Progressive motor dysfunction leads to dorsiflexion. Abnormality in autonomic function causes orthostatic hypotension, gastro paresis, bloating, nausea and diarrhea. Indeed, autonomic markers in diabetic individuals have the poorest prognosis following myocardial infarction (Barthel *et al.,* 2011).

2.8.4 Ischemic Heart Disease (IHD) and Cerebrovascular Disease (CVD):

Diabetes Mellitus increases the risk of myocardial infarction in comparison to the person who is non-diabetic (Haffner *et al.,* 1998). More than 50% of the mortality is seen due to IHD accounts for diabetic population (Laing *et al.,* 2003_a) and compared to the general population DM approximately increases the risk of myocardial infarction by threefold (Domanski *et al.,* 2002). IHD in diabetes include premature atherosclerosis leading to myocardial infarction and stroke,

impaired cardiac function, which is predominantly diastolic dysfunction (Okon *et al.,* 2005). Atherogenesis causes immune cells including macrophages and T cells to bind to the vessel wall (O'Brien *et al.,* 1996). Foam cell and fatty streak are formed due to movement of low-density lipoprotein into the sub endothelial space (Glass and Witztum, 2001) that is often seen in bifurcations, branches, and curves (Ross,1995). Diabetic cardiomyopathy is termed when damage to the myocardium in the absence of hypertension and coronary artery disease occur (Boudina and Abel,2007; Rubler *et al.,* 1972). Diastolic dysfunction is the characteristics of Cardiomyopathy which is an inability of the heart to relax and undergo filling during the diastole of the cardiac cycle (Kannel *et al.,* 1974; Rakowski *et al.,*1996).Long-term glycemic control measures by HbA1C, remains the best predictor of IHD risk in both type 1 and type 2 diabetic individuals (Borg *et al.,* 2010; Cederberg *et al.,* 2010).Oxidative stress and chronic inflammation alter the gene expression within the vasculature (Feng *et al.,* 2005). There is also vascular repair failure of in diabetes,with a decrease in endothelial progenitor cells ultimately significant morbidity and early mortality seen in both major forms of diabetes (Tepper *et al.,* 2002; Dessapt *et al.,* 2010).

2.9 Common mechanism of damage:

2.9.1 Glucose: The Master Switch:

2.9.1.1 Controlling blood glucose: Hyperglycemia is the major diagnostic biochemical parameter in both Type 1 diabetes and T2DM (Figure 1). Achieving optimal glycemic control is the most effective way to reduce the risk for vascular complications.

2.9.1.2 Losing control of energy production: Cells like endothelial cells are prone to diabetic complications, which ultimately become unable to modulate glucose transport rates and can't prevent excessive accumulation of intracellular glucose.

Hence, energy production in these cells becomes uncontrolled in the context of diabetes and eventually is impaired (Figure 2).

2.9.1.3 Hexosamine biosynthesis: An important enzyme Glucokinase/hexokinase is involved in the transport of glucose into cells.

2.9.1.4 Aldose reductase: Increased flux through the sorbitol/polyol pathway, NAD (P)H delivered from the pentose phosphate pathway where intracellular accumulation of sorbitol can result in osmotic stress damaging proteins via oxidation reactions.

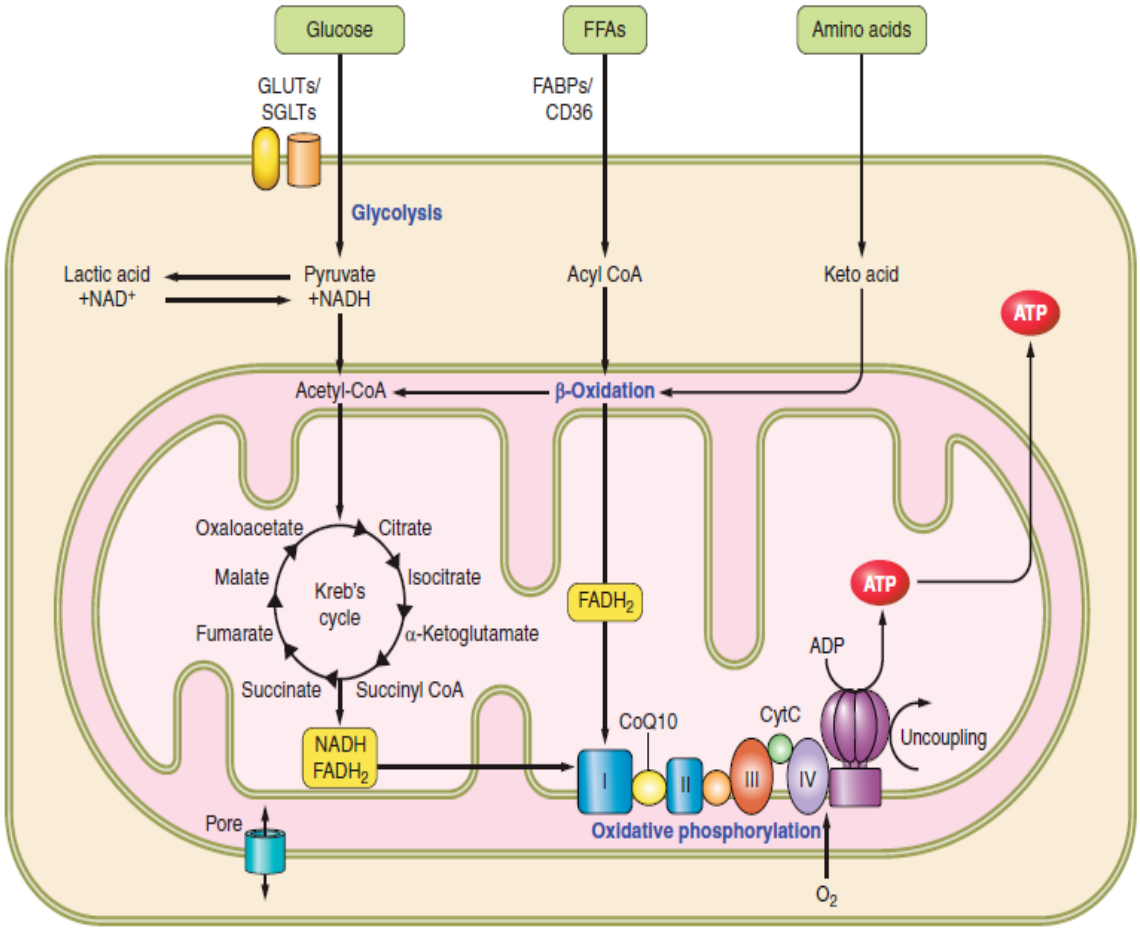


Figure 2: Overview of fuel production within the mitochondria. NAD/H, nicotinamide adenine dinucleotide (reduced); FADH2, flavin adenine dinucleotide (reduced); I, complex I (NADH dehydrogenase); II, complex II (succinate dehydrogenase); III, complex III (cytochrome *c* reductase); IV, complex IV (cytochrome-*c* oxidase); mPT, mitochondrial pore; CoA, coenzyme A.

2.9.1.5 Insulin resistance: Loss of cellular signaling in response to the hormone insulin is defined as insulin resistance. Skeletal muscle, adipose tissue and liver tissues are most affected by reductions in insulin sensitivity, although there are other cells which also depend on insulin-mediated glucose uptake (Forbes and Cooper, 2013).

2.9.2 Obesity

2.9.2.1 Nutrient overload: Common co-morbidity seen in type 2 diabetes individuals is Obesity. Obesity is known to exacerbate the development of diabetic complications This is likely due to the concomitant abnormalities seen in nutrient and calorie overload, insulin sensitivity, and secretion, with the addition to lack of physical activity, which all are likely the contributors to vascular complications.

2.9.2.2 Adipokines: Adipose tissue is the highly secretory, which releases a number of factors that a modulated in response to hyperglycemia. Adipokines have been shown direct effects on organs which are susceptible to T2DM complications (Forbes and Cooper, 2013).

2.9.3 Lipids:

2.9.3.1 Dyslipidemia: Dyslipidemia includes raised plasma triglycerides and LDL-cholesterol, in the context of decreased HDL-cholesterol.

2.9.3.2 Lipid lowering: Most prominent effects of lipid lowering in diabetic individuals are seen on their cardiovascular disease risk. Here statins (A class of lipid lowering agent) are thought to have broad-ranging benefits in diabetic individuals, whether fenofibrates (Another class of lipid lowering agent) have shown inconsistent results (Forbes and Cooper, 2013).

2.9.4 Blood Pressure and Hemodynamic:

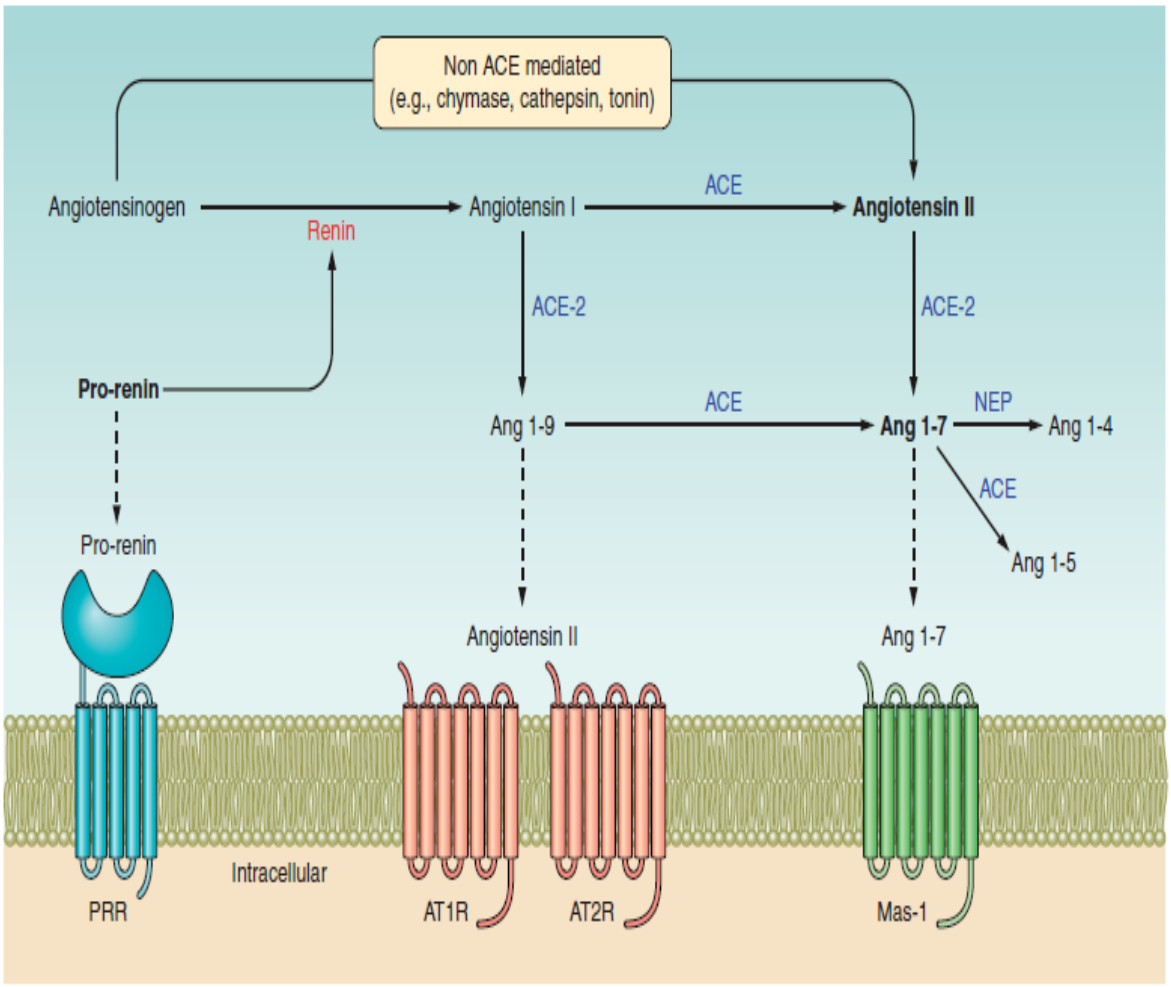


Figure 3: The renin-angiotensin cascade. ACE, angiotensin converting enzyme; NEP, natriuretic peptide; Ang, angiotensin (Forbes and Cooper, 2013. pp 147). .

2.9.4.1 Introduction: Hemodynamic factors contribute to the development and, particularly, the progression of diabetic complications. These hemodynamic factors include tissue-derived and systemic components of the Renin-angiotensin-aldosterone system (RAAS; Figure 3). The clinical studies show systemic hypertension is commonly associated with accelerated vascular complications including nephropathy, retinopathy macrovascular and disease (Forbes and Cooper, 2013).

2.9.4.2 The Renin-Angiotensin-Aldosterone System (RAAS): The hormonal system RAAS is considered as a master controller of blood pressure and fluid balance in the body. Organs prone to diabetic complications appear to have their own functional tissue RAAS(Forbes and Cooper, 2013) .

2.9.5 Protein Modifications and Turnover

2.9.5.1 Protein folding: The folding of translated linear strands of amino acids into a fully functional three-dimensional protein is one of the most complex processes which occurs within cells. Misfolded proteins can occur as a consequence of a number of different processes like genetic mutations and interruption of posttranslational modifications (Forbes and Cooper, 2013) .

2.9.5.2 Autophagy: A cellular process causing breakdown of proteins into their constituent amino acids during times of need in metabolic disorders is called Autophagy. Autophagy is seen in diabetes, so, changes in autophagy could facilitate the use of inappropriate fuels for energy production, commonly seen at sites affected by diabetic complications.

2.9.5.3 Posttranslational modifications: Through following process.

a) N-linked glycosylation: *N*-linked Glycosylation is a type of enzymatic posttranslational modification which results in the addition of glycans onto lipids, proteins and other organic molecules.
b) O-linked glycosylation: It is a late posttranslational process occurs within Golgi apparatus.
c) Advanced glycation: It is a non-enzymatic posttranslational modification which begins with covalent attachment of heterogeneous sugar moieties is called Advanced glycation. It occurs to free amino groups on proteins and amino acids.
d) Phosphorylation: Phosphorylation is one of the pathways implicated in the development of diabetic complications which involves activation of the key intracellular second messenger protein kinase C (PKC) (Forbes and Cooper, 2013).

2.9.6 Redox Imbalances

2.9.6.1 The mitochondria: Superoxide (O_2^-) generation by dysfunctional mitochondria in diabetes has been postulated as the primary initiating event in the development of diabetic complications.

2.9.6.2 NAD (P) H oxidase: NAD (P) H oxidase was originally discovered in neutrophils where it produces vast quantities of $O2^-$ by electron transport to augment host-pathogen defenses.

2.9.6.3 Nitric oxide synthase (NOS): Nitric oxide is a common free radical which causes vascular dilatation following its release from endothelial cells. Indeed, it is one of the most powerful vasodilators and is generally thought to be vasoprotective in the context of diabetes.

2.9.6.4 Antioxidants: There is consistent evidence in organs affected by diabetic microvascular disease that, the expression and activity of antioxidant enzymes is altered. Over expression of catalase in experimental models of type 2 diabetic nephropathy also appears to be protective (Forbes and Cooper, 2013).

2.9.7 Inflammation

2.9.7.1 Introduction: An integral part of innate immunity is acute inflammatory response, which is triggered in response to a perceived or real threat to tissue homeostasis. Here the innate immune response is relatively nonspecific. The adaptive immunity allows the human body to recognize and remember pathogens. This results in the ability of enhancing inflammatory response following re-exposure to a specific pathogen (Forbes and Cooper, 2013).

2.9.7.2 Adhesion molecules: Hyperglycemia, Dyslipidemia and hypertension induce activation of the endothelium which results in inflammation via a variety of mechanisms at the sites of diabetic complications.

2.9.7.3 Leukocyte infiltration: In response to chemotactic molecules, Phagocytic cells such as macrophages and monocytes are often the first infiltrating cells which arrive at sites of diabetic complications.

2.9.7.4 Inflammatory cytokines: Cytokines are a complex group of molecules which are capable of triggering differential effects on cells that depends on factors such as cell type, timing. In that context it is likely that cytokines and their receptors have difficulties to target therapeutically given that it may alter many times over the course of the development and progression of diabetes complications by their temporal expression (Forbes and Cooper, 2013).

2.9.7.5 Growth factors: Insulin is one of the major growth factor associated with tissue survival and growth. Hyperinsulinemia is associated with organ and tissue hypertrophy. It is seen that hypertrophy and hyperplasia are most common at the major peripheral insulin signaling sites such as the skeletal muscle, liver and adipose tissue. This is suggested that there are a range of insulin-related effects on the development and progression of diabetic complications. In case of diabetic neuropathy, there are some evidence implicating members of the Insulin like Growth Factor-I axis as pathological mediators of hypoalgesia and peripheral neuropathy.

2.9.7.6 Cyclooxygenase: Cyclooxygenase (COX) enzymes facilitate the formation of prostanoids, such as prostacyclin, prostaglandins and thromboxane where the expression of COX-2 is stimulated by inflammation and mitogens.

2.9.7.7 NF-κB: NF-κB ,a transcription factor is thought to be an important modulator of diabetic complications.

2.9.7.8 Toll-like receptors: In both adaptive and innate immunity Toll-like receptors (TLRs) play a role. They are thought to be central modulators of a number of infectious diseases, pathological conditions, autoimmune and neurodegenerative diseases. In the development of T2DM complications, role of TLRs comes from studies performed in rodent models where these receptors have been deleted (Forbes and Cooper, 2013).

2.9.8 Gene Regulation

2.9.8.1 Metabolic memory: The hyperglycemic contribution to macrovascular disease needs to be reconsidered in the context of clinical trials exploring the effects of strict glycemic control in T2DM subjects with established CVD (Forbes and Cooper, 2013).

2.9.8.2 Histone modifications: Remodeling of chromatin, a complex of DNA and histone proteins firstly by posttranslational protein modifications of the histone tails by processes such as methylation, acetylation, ubiquitylation, advanced glycation, and phosphorylation. Secondly by direct modification of DNA by the adding methyl groups. Each of these modifications alters the DNA structure exposing or concealing specific gene sequences ultimately enhance or inhibit gene transcription (Forbes and Cooper, 2013).

2.9.8.3 Sirtuins: The sirtuin family of proteins known as sir-2 is categorized as class III histone deacetylases which plays complex and important roles in ageing-related pathological conditions

such as dysregulation of metabolism. Sirtuins can affect gene apoptosis, transcription and resistance to stress, also modulate energy efficiency during restricted calorie intake.

2.9.8.4 MicroRNA: Short sequences of RNA which directly bind complementary mRNA is MicroRNAs, that arrests their translation into protein or targeting these mRNAs for degradation (Forbes and Cooper, 2013).

2.10 Factors associated with T2DM

2.10.1 Hypertension (HTN):

Hypertension is an important associated factor related to T2DM complications.

Hypertension is diagnosed when a person's Systolic Blood pressure (SBP) is ≥140 mm (Hg) and/or Diastolic Blood Pressure (DBP) is ≥90 mm (Hg) following repeated setting (Thomas *et al.,* 2020).

2.10.2 Dyslipidemia:

Dyslipidemia may be defined as unwanted levels of one or more of following lipid particles in the blood; high-density lipoprotein (HDL), low-density lipoprotein (LDL), triglycerides (TG) and total cholesterol. It could be explained as disorder of lipoprotein metabolism. It could be either hyperlipoproteinemia or hypolipoproteinemia (Kolovou *et al.,* 2005). Increasing level of atherogenic lipid particle and immunogenic lipid particles such as LDL, triacylglycerol, cholesterol and low density lipoprotein and lower plasma level of HDL are the indicators of dyslipidemia (Lima *et al.,* 2011). The following level of serum lipid particles are considered as normal: Total cholesterol ≤ 200 mg/d, HDL ≥ 40 mg/dL, LDL ≤ 100 mg/dL , Triglycerides ≤ 150 mg/dL and change in the following lipid particle levels are considered as dyslipidemias (Hoffman, 2021).

2.10.3 Body Mass Index (BMI):

Body mass index (BMI) is a value derived from the mass (weight) and height of a person. It is defined as the body mass divided by the square of the body height, and is expressed in units of kg/m2, resulting from mass in kilograms and height in meters. The BMI is expressed in kg/m2, resulting from mass in kilograms and height in meters. If pounds and inches are used, a

conversion factor of 703 (kg/m2)/(lb/in2) is applied. When the term BMI is used informally, the units are usually omitted. The formula is given below.

$$\mathrm{BMI} = \frac{\mathrm{mass_{kg}}}{\mathrm{height_m}^2} = \frac{\mathrm{mass_{lb}}}{\mathrm{height_{in}}^2} \times 703$$

(Anannya$_b$, 2019)

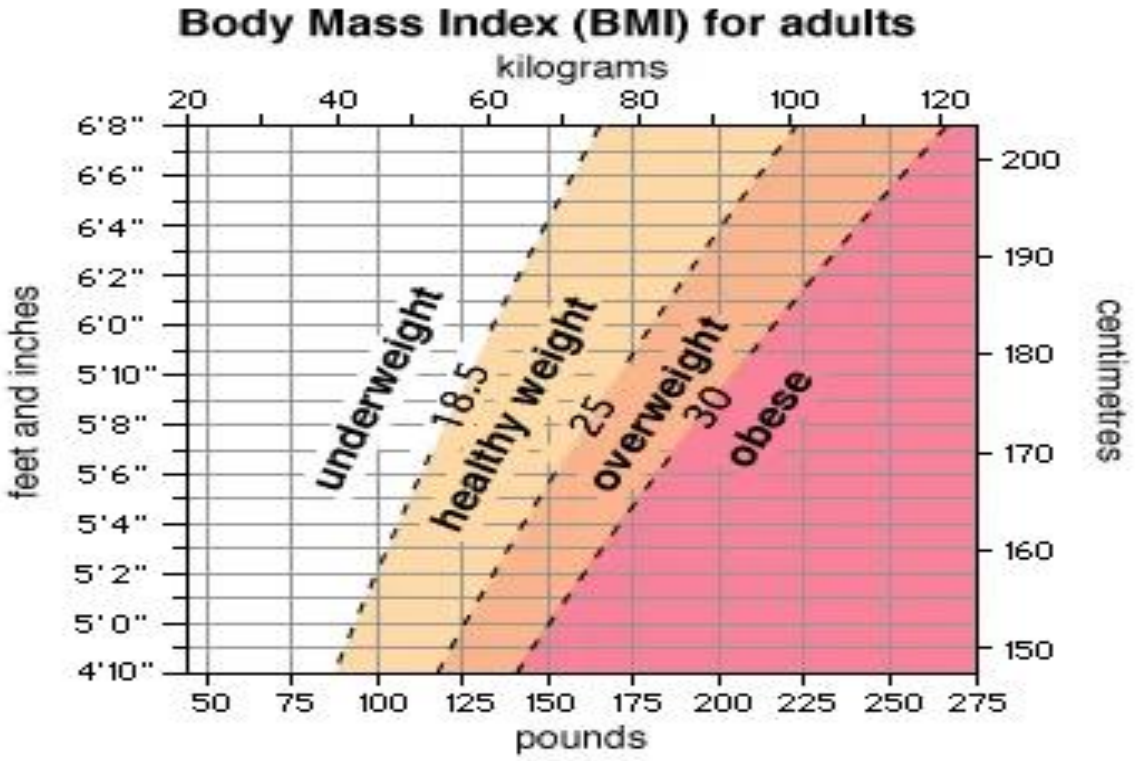


Figure 4: BMI chart for adults

Category of the individual according to BMI (kg/m2):

1. Underweight : <18.5
2. Normal range : 18.5 – 24.9
3. Overweight (Pre-obese) : 25.0 – 29.9
4. Obese (Class I) : >30.0 (Anannya$_b$, 2019)

2.11 Diabetic complications: Global picture

As T2DM is a global issue, so the complications regarding DM are also burning and issue of interest for many research workers around the world. This has already been studied in different countries all over the world. In a Ethiopian study the percentage of complications related to

T2DM were Cardiovascular disease 37%, Eye disease 36.4%, HTN and renal disease 35.4 and impotency 23.4% (Gizaw *et al.,* 2019). Another study in Northern Africa (Tunisia, Egypt & Sudan) from January 1990 to July 2012 showed that, the prevalence of complications are higher in urban area than rural area, and the T2DM patients suffered from diabetic retinopathy ranging from 8.1% to 41.5%, Diabetic Nephropathy ranging from 6.7% to 46.3% and Diabetic neuropathy ranges from 21.9% to 60% (Bos and Agyemang ,2013**).** In Diabetics Clinic of the Komfo Anokye Teaching Hospital, Kumasi, Ghana a study was done, which reflects 76.8% of the diabetic patients had some types of complication which includes hypoglycemia (37.9%), peripheral artery disease (3.8%), Diabetic Nephropathy (25.9%) and multiple complications (0.4%). The study also showed that, these complications were prevalent more in females (42.7%) compared to males (34.1%) (Sarpong ., *et al.,* 2017). A community-based study was carried out in a rural setting in Goa, India in 2011which also showed Diabetic neuropathy (60%), CVD (32.3%) and Diabetic retinopathy (15.4%), Peripheral arterial disease (11.5%) and cerebrovascular disease (6.9%) (Nafisa *et al.,* 2011). An European study shows the crude prevalence of microvascular complications were 18.8% and macrovascular complications were 12.7% where, the common microvascular complications showed peripheral neuropathy (7.7%), chronic kidney disease (5.0%) and common macrovascular complications were cardiovascular disease (8.2%) and cerebrovascular disease (2.2) (Kosiborod *et al.,* 2018). In Latin America a cohort study over one thousand six hundred and sixteen patients showed macrovascular complications in 13.8% of the subjects and microvascular complications in 15.2% patients. HTN and Dyslipidaemia were found in 55.5% and 45.9%, respectively (Chih *et al.,* 2019). Several studies in Latin American countries such as in Mexico in the year 2012, 47.6% diabetic patients reported impaired vision where 6.6% lost their visual site and needed hospitalization and other had chronic renal insufficiency and non-traumatic amputations and also there was high prevalence of obesity in 17.5% of the male and 25.2% of the female population. Argentinian study from year 2005-13 also showed the number one cause of non-traumatic blindness as diabetic retinopathy and diabetes became the leading cause of dialysis for 34.7% of incidental cases and 22.8% of renal failures. In 2016-17 Chilean study also showed the significance of diabetic nephropathy where 35% of all cases of advanced chronic renal failure were known to be related to T2DM (Sinisterra *et al.,* 2019).

Methods and Materials

Chapter III: Methods and Materials

3.1 Study area:

People's Republic of Bangladesh is a highly populated country situated in the south East Asia with about 170 million populations. In Bangladesh Chattogram is the second largest city. It is situated in the south-east part of country at the bank of the river Karnaphully. The population of the city is around 6 million. As the author is from the city and no specific study regarding T2DM complications were significantly done in previous time in Chattogram, so this city was chosen as study area.

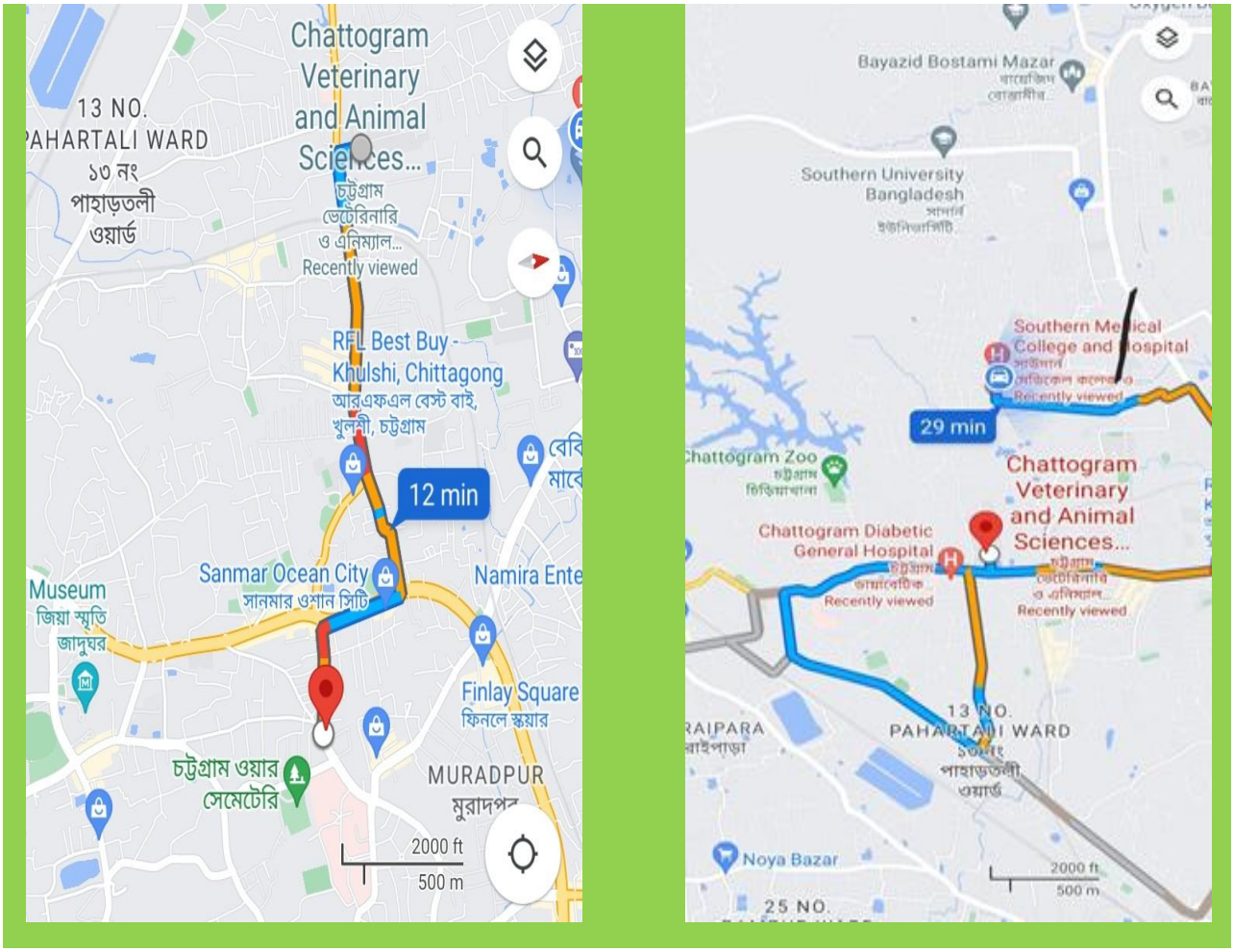


Figure 4: Map of the study area locating Chattogram Diabetic General Hospital, Southern Medical College Hospital, Chattogram Veterinary and Animal Sciences University and Author's personal chamber location.

3.2 Study period:

It was a cross sectional study which conducted for a period of one year from October 2020 to September 2021. Initially study period was from January 2020 to June 2020. But due to COVID-19 pandemic situation, the author couldn't start the research work. Then the work has been again started from October 2020 and with frequent interruption due to COVID-19 second and third wave, the data collection ultimately ended on October 2021.

3.3 Participants of the study:

The target population for the study was the outdoor patients in Chattogram Diabetic General Hospital (CDGH) but after starting the study due to second wave of COVID-19 pandemic, the author had to reset the target population. Finally the data had been collected from Chattogram Diabetic General Hospital (CDGH), Author's personal Chamber and Southern Medical College Hospital (SMCH), Chattogram.

3.4 Sample size:

Primarily the sample size was 200, but at the end of the study period, the author couldn't collect more than 158 samples.

3.5 Definitions:

3.5.1: Type 2 Diabetes Mellitus:

Commonest type of diabetes is Type 2 diabetes Mellitus considering over 90% of all Diabetes Mellitus cases. It is a disease that occurs when blood glucose (blood sugar) is too high. A pancreatic hormone named insulin helps glucose get into cells for producing energy. In case of type 2 diabetes, body doesn't use insulin well or doesn't make enough insulin to reduce the glucose level in blood in the result of insulin resistance. Thus too much glucose stays in blood, and not enough reaches into cells. If a person's fasting blood glucose is ≥7.0 mmol/lit (126 mg/dl) or 2 hours after 75gm Glucose intake the blood glucose is ≥11.1 mmol/lit (200 mg/dl), then the person will be diagnosed as a case of Diabetes Mellitus. A person can develop T2DM at any age, even during childhood. Usually T2DM occurs most often in older adults. Common risk factors of developing T2DM are Family history of diabetes, Physical inactivity, Overweight,

Increasing age, Unhealthy diet, Ethnicity (Pima and Navajo Native Americans, Aboriginal and Torres Strait Islander in Australia, Canadian First Nation people, Asian and Afro-American Descent) , High blood pressure, History of gestational diabetes, Impaired fasting (Fasting Blood Glucose 6.1mmol/lit to 6.9 mmol/lit) or Impaired glucose tolerance (2HA75gm Glucose blood glucose level is 7.9 mmol/lit to 11.0 mmol/lit), Poor nutrition during pregnancy.

3.5.2 T2DM complications:

Complications of diabetes mellitus mean the problems which develop over time and may affect different systems of the body and resulting in deterioration of different organ or system functions. The complications of T2DM can affect the quality of life and cause lifelong disability. The complications are categorized into: a) Macrovascular complications and b) Microvascular complications.

a) Microvascular complications:

i) Diabetic Retinopathy: Diabetic retinopathy (DR) is a common cause of blindness in adults. Hyperglycemia increases retinal blood flow and metabolism, and has direct effects on retinal endothelial cells, resulting in impaired vascular auto regulation. This leads to chronic retinal hypoxia, which stimulates production of growth factors and causes new vessel formation and increased vascular permeability (Innes, 2020).

ii) Diabetic Nephropathy: T2DM may present with albuminuria at the time the diabetes is detected. Due to T2DM structural and functional changes occur in the kidney which results in proteinuria, hypertension, and progressive reduction of kidney function. This is the hallmark of diabetic nephropathy (Ron and Jialal, 2021).

iii) Diabetic Neuropathy: Diabetic neuropathy is nerve damage that can occur in people with diabetes. Different types of nerve damage cause different symptoms. Symptoms can range from pain and numbness in your feet to problems with the functions of your internal organs, such as your heart and bladder. Diabetic neuropathy is nerve damage that is caused by diabetes. Over time, high blood glucose levels, also called blood sugar, and high levels of fats, such as triglycerides, in the blood from diabetes can damage your nerves. Symptoms depend on which type of diabetic neuropathy you have. Diabetic neuropathy is grouped into: **a) Peripheral neuropathy** (Type of nerve damage that typically affects the limbs specially feet and legs and sometimes affects the hands and arms. This is commonest type of neuropathy

affecting Up to one-half of T2DM population. **b) Autonomic neuropathy** (Damage to nerves that control the internal organs leading to problems with heart rate and blood pressure, gastrointestinal system, Urinary bladder, sexual organs, sweat glands, eyes, low blood glucose or low blood sugar or hypoglycemia unawareness). Long standing high blood glucose or blood sugar and high levels of lipids (e.g. triglycerides) damage nerves and the small blood vessels that nourish nerves, leads to diabetic neuropathies (NIDDK, USA).

b) Macrovascular complications:

i) Ischemic Heart Diseases (IHD): Ischemic Heart Diseases (IHDs) are a group of disorders of the heart and blood vessels. They include: Coronary artery disease (A disease of the blood vessels supplying the heart muscle), Deep vein thrombosis and pulmonary embolism (Blood clots in the leg veins, which can dislodge and move to the heart and lungs. The most common reason for this is a build-up of fatty deposits on the inner walls of the blood vessels that supply the heart.

ii) Cerebrovascular disease (CVD): A disease of the blood vessels supplying the brain leading to Transient ischemic attack (TIA) and Stroke (Usually acute events and are mainly caused by a blockage that prevents blood from flowing to the brain).Strokes can be caused by bleeding from a blood vessel in the brain or from blood clots. The most common reason for this is a build-up of fatty deposits on the inner walls of the blood vessels that supply the brain. (WHO, 2021)

iii) Peripheral arterial disease: A disease of blood vessels supplying the arms and legs leading to pain in thigh, calf, or buttocks that happens during walking due to fat deposition in peripheral blood vessels causing of oxygen supply leading to cell death (Editorial, 2022).

3.5.3 T2DM associated risk factors:

a) **Hypertension:** Hypertension is an important associated factor related to T2DM complications. Hypertension is diagnosed when a person's Systolic Blood pressure (SBP) is ≥140 mm (Hg) and/or Diastolic Blood Pressure (DBP) is ≥90 mm (Hg) following repeated setting (Unger *et al.*, 2020).

b) **Dyslipidemia:** Dyslipidemia may be defined as unwanted levels of one or more of following lipid particles in the blood; high-density lipoprotein (HDL), low-density lipoprotein (LDL), intermediate density lipoprotein (IDL), very low-density lipoprotein (VLDL), triglycerides (TG), total cholesterol and others. It could be explained as disorder of lipoprotein metabolism. It could be either hyperlipoproteinemia or hypolipoproteinemia (Kolovou *et al.*, 2005). Increasing level of atherogenic lipoprotein particle in blood plasma and immunogenic lipid particles such as LDL, triacylglycerol, cholesterol and small density lipoprotein and lower plasma level of HDL are the indicators of dyslipidemia (Lima *et al.*,2011). The following level of serum lipid particles are considered as normal: Total cholesterol ≤ 200 mg/d, HDL ≥ 40 mg/dL, LDL ≤ 100 mg/dL, Triglycerides ≤ 150 mg/dL and change in the following lipid particle levels are considered as dyslipidemias (Hoffman, 2021).

c) **Body Mass Index (BMI):** Body mass index (BMI) is a value derived from the mass (weight) and height of a person. It is defined as the body mass divided by the square of the body height, and is expressed in units of kg/m2, resulting from mass in kilograms and height in meters. The BMI is expressed in kg/m2, resulting from mass in kilograms and height in meters. If pounds and inches are used, a conversion factor of 703 (kg/m2) / (lb. /in2) is applied. When the term BMI is used informally, the units are usually omitted. BMI ≥ 25 following the given formula has risk to develop T2DM.

$$\mathrm{BMI} = \frac{\mathrm{mass_{kg}}}{\mathrm{height_m}^2} = \frac{\mathrm{mass_{lb}}}{\mathrm{height_{in}}^2} \times 703$$

(Anannya$_b$, 2019)

3.6 Study design:

It was a cross sectional studies for the assessment of prevalence of Type 2 diabetes mellitus complication in human in Chattogram city. The data was collected from the T2DM patient, who came to Chattogram Diabetic General Hospital (CDGH), Author's personal Chamber and Southern Medical College Hospital (SMCH), Chattogram. All T2DM patients fulfilling the inclusion criteria were invited to take part in the study with their written consent.

The inclusion criteria were:

1. Diagnosed case of T2DM according to the International standard by American Diabetic Association (ADA) [https://www.diabetes.org/diabetes/a1c/diagnosis]
2. Under regular anti diabetic treatment
3. Provided written inform consent in the selected area in the Questionnaire.

The study was approved by CVASAU ethical approval committee {Memo no.- CVASU/Dir (R &E)EC/2019/126(10) on Date 29/12/2019}.

3.6.1 Survey:

1. Detailed information regarding the study was provided to all eligible individuals. Person only who agreed to participate and sign in the consent part were included in the study. Subjects were interviewed face to face using a pre-structured questionnaire by the author himself to gather the information regarding demographic details, physical examination, diabetic history and medications, associated risk factors, present diabetic problems or complications, life style and available necessary laboratory reports of biochemical markers associated with Diabetes (Which the patient could provide instantly and easily).

2. Questionnaire information:

a) Serial no. : A serial number was given for individual participant.
b) General information of the participant: Date of interview, patients ID (CDGH, Chamber, SMCH), Name, Age, Sex, Address, Location/Living, Marital status, Occupation, Educational status, Type of family, Family member, Religion, Monthly income, Attendant and Contact number was taken.
c) General examination: Blood pressure, Height in cm, Weight in Kg , BMI was taken. Pulse, Temperature, Respiratory rate.

d) Diabetic history and medication: How long have been suffering from diabetes, How did find out diabetic, Specification of the sugar level at the time of Diagnosis (FBS & or 2HAB), Diabetes knowing, Type of therapy taking for Diabetes Mellitus. Mentioning Oral Anti-diabetic Drug(OAD), From when have started taking insulin ,Who gives the injection , Checking CBG each time before taking insulin, Injection sites are used , Reuse your syringes, had hypoglycemic attack from extracorporeal Insulin, Required assistance or hospitalization for it or not, any additional nutritional supplements.

e) Information regarding risk factors for a diabetic patient: Family history of Diabetes Mellitus, Smoking status, Alcohol consumption status, Other medication history, having any anxiety or not with mentioning which environment, Having sound sleep or not, Daily sunlight exposure, happiness are you with your economic solvency (According to participants view of he/she is happy or not)

f) Chronic macrovascular and microvascular complications regarding T2DM (Eye problems, Ear problems, Cardiac problems, Respiratory problems, Burning problems, Stroke history, Teeth/Gum problems, Feet/leg problems, Skin problems, Gastrointestinal problems , Sexual dysfunction, Kidney problems, Liver problems, ,Psychological problems, Thyroid problems, Frequent infections, any surgery regarding DM, Allergic problems, Bones & Joints pain, any malignancy, other metabolic problems) and also T2DM associated risk factors (Hypertension, Dyslipidemias) with their duration. Here there is also a column in the questionnaire for laboratory values of biochemical markers associated with T2DM complications such as Total S. Cholesterol, S. triglycerides , S. creatinine, SGPT, S.TSH.

g) Diabetes Self Care Behaviors: Performing daily physical activity, Following any diet plan, Weight changed in the past three months, Number of eating per day, From where is the meal, Appetite describing, Regular testing blood for sugar, How often tested, Record keeping or not, How often having HIGH blood sugar, How often having LOW blood sugar ,Testing urine for sugar or ketones, Eyes checking by an eye doctor, Feet checking at home, Dental checkup history, Blood pressure checkup history, Cholesterol and triglycerides checkup history, HbA1c test history with value (if any).

h) Declaration of the participant

3.6.2 Statistical analysis:

The gathered information was entered into MS-Excel-2010, coded, decoded, sorted out and exported to Statistical Package for Social Sciences version 26. Descriptive statistics were performed including mean, SD, minimum, maximum, 95% CI and percentage, t-Test, Chi square test, correlation and multiple linear regression analysis were performed. The $p < 0.05$ was considered significance.


Results

Chapter IV: Results

4.1 The overall socio demographic, life style behavior and general health information of T2DM individuals:

For T2DM individuals the most important information regarding the complications and associated factors are the analysis of their socio-demographic status, life style behavior, general health characteristics and therapy taken for T2DM. These are being discussed below.

4.1.1 Socio-Demographic information of T2DM patients:

In the very beginning the basic information are discussed. Socio-demographic information of the Type 2 Diabetes Mellitus are depicted in table 4 which shows, highest (55.7%) participants are from author's personal chamber and lowest (13.9%) from Chattogram Diabetic General Hospital (CDGH). Of the total studied individuals (n=158) 54.4% are female and 45.6% are male. As expected highest number (62.1%) of participant were from urban and lowest number (1.8%) are living in overseas. Almost 84% are married and rests of them are either single or divorced or widowed. 50% participants don't do any job, 21.5% are job holder, 17.7% are businessmen, 2.8% are farmers and rest are retired. On the basis of educational status, 24.6% completed Honors and above, 8.9% illiterate, 20.9% completed primary and rest have completed either SSC or HSC. The proportion of living in nuclear family is higher (51.9%) than joint family (48.1%). As the highest number of participants from author's personal chamber and author couldn't collect the data from Chattogram Diabetic General Hospital due to COVID-19 pandemic, so majority of the participants were Muslims (94.4%), 4.4% were Hindus, 0.6% was Christian and 0.6% was Buddhist which actually doesn't reflect the national ratio of religion in Bangladesh.

Table 4: Socio-Demographic information of T2DM patients (N-158)

Variable	Category	n	%
Patient's source	CDGH	22	14
	Author's personal chamber	88	56
	SMCH	48	30
Sex	Male	72	46
	Female	86	54
Residence Type	Urban	98	62
	Slum	16	10
	Rural	41	26
	Overseas	3	2
Marital Status	Single	5	3
	Married	133	84
	Divorced	3	2
	Widowed	17	11
Occupation	Don't do job	79	50
	Job holder	34	22
	Businessman	28	18
	Farmers	6	4
	Retired	8	5
	Other	3	1
Educational Status	Illiterate	14	9
	Primary	33	21
	SSC	32	20
	HSC	40	25
	Honors and above	39	25
Family Structure	Nuclear	82	52
	Joint	76	48
Religion	Muslim	149	94
	Hindu	7	4
	Christian	1	1
	Buddhists	1	1

Note: CDGH= Chattogram Diabetic General Hospital, SMCH= Southern Medical College Hospital, SSC= Secondary school Certificate, HSC= Higher Secondary Certificate

4.1.2 Life style & behavior of T2DM patients:

The next important part regarding basic information of a T2DM patient is the lifestyle and behavior pattern (Table 5) of the total participants, almost 75% had never smoked and 20% were former and rest were current smokers. 95% never consumed alcohol, 2.5% were former and 2.5% were occasional alcohol consumer. Only 13.3% individuals don't perform daily exercise and rest do minimum 30 mins brisk walk per day. Nearly 20% don't follow any diet chart and rest follow diet chart either by diabetologist, or internet or self-implicated. As expected 121(76.6%) participants have anxiety and the rest have not, 62.7% don't have sound sleep and rest have. Regarding daily sunlight exposure statement, 61 (38.6%) don't go for daily sunlight exposure and the rest 97 (61.4%) have daily sunlight exposure varying the duration from few hours to 6-8 hours. Almost 53% participants were neither happy nor un-happy, 26 (16.5%) were unhappy, 7 (4.4%) were very unhappy and rest participants were happy or very happy. On the context of study regarding prevalence of complications of T2DM, family history is an essential part of a study. In this study 16.50% participants showed no family history of T2DM, 15.8% have father having T2DM, 24.1% have mother having T2DM, near 14% have both father and mother have T2DM and the rest 29.7% have Brother, sister and other 1^{st} degree family members having history of T2DM.

Table 5: Life style & behavior (N=158)

Variable	Category	n	%
Smoking status	Never	119	75.3
	Former	32	20.3
	Current	7	4.4
Alcohol consumption status	Never	150	95
	Former	4	2.5
	Current	0	
	Occasional	4	2.5
Performing physical exercise everyday:	No	21	13.3
	Heavy(brisk walk>90mins)	7	3.7
	Moderate(brisk walk60-90mins)	31	20
	Mild (brisk walk 30-59mins)	56	36
	Sedentary(brisk walk<30mins)	43	27
Diet plan:	No	32	19.9
	By Diabetologist	36	23.1
	Through internet	2	1
	Self-implicated	88	56
Do you have any anxiety?	Yes	121	76.6
	No	37	23.4
Having sound sleep:	Yes	59	37.3
	No	99	62.7
Daily Sun exposure	No	61	38.6
	Yes	97	61.4
Happy/Unhappy:	Very unhappy	7	5.5
	Unhappy	26	16.5
	Neither happy nor unhappy	84	54
	Happy	38	24
Family history of T2DM	Father	25	15.8
	Mother	38	24.1
	Father & Mother	22	13.9
	Brother, sister & other 1st degree family member	47	29.7
	No family history	26	16.5

Note: T2DM= Type 2 Diabetes Mellitus

4.1.3 General Health information of T2DM patients:

A T2DM patient should regularly monitor his/her Blood pressure, BMI, basic biochemical tests regarding T2DM (Table 6), where the participants Systolic blood pressure ranging 100-210mm (Hg) [95%CI, 127.32~132.93] and Diastolic blood pressure ranging 40-130mm (Hg) [95%CI, 80.08~83]. BMI was ranging 18-44 (95% CI, 25.76~27.06). Of the total participants, 35 participants provided their biochemical values of there, the mean of total Serum Cholesterol was averaging 207 mg/dL which ranging 102-315mg/dL (95% CI, 199.60~213.78) and Triglycerides averaging 241 mg/dL with range of 134-484 mg/dL (95% CI, 226.57~255.31). OF 158 individuals 22 showed their serum creatinine value ranging 1-3 mg/dL (95% CI, 1.22~1.41) with an average of 1.32mg/dL. Total 13 participants gave SGPT laboratory value averaging 49 Unit/Lit, ranging 13-87 Unit/Lit (95% CI, 45.94~52.36) and 09 participants gave S. TSH laboratory value averaging 9.73 mU/Lit which ranging 9 to 2 mu/Lit (95% CI, 8.06~11.4).

Table 6: General Health information (n=158)

Variable	n	Min	Max	Mean ± SD	95% *CI*
Systolic BP (mm of Hg)	158	100	210	130.13 ± 18.21	127.32~132.93
Diastolic BP (mm of Hg)	158	40	130	81.74 ± 10.70	80.08~83.4
BMI (Kg/m^2)	158	18	44	26.41 ± 4.18	25.76~27.06
Height (cm)	158	137	188	161.41 ± 9.24	159.98~162.84
Weight (Kg)	158	43	110	68.90 ± 11.56	67.09~70.70
Total S. Cholesterol (mg/dL)	35	102	315	206.69 ± 45.50	199.60~213.78
Triglycerides (mg/dL)	35	134	484	240.94 ± 92.08	226.57~255.31
S. creatinine level (mg/dL)	22	1	3	1.32 ±.59	1.22~1.41
SGPT level (Unit/Lit)	13	26	87	49.15 ± 20.58	45.94~52.36
S. TSH level (mU/Lit)	9	2	30	9.73 ± 10.67	8.06~11.4

Note: Min=Minimum, Max = Maximum, BP= Blood Pressure, BMI= Body Mass Index, cm= centimeter, Kg=Kilogram, SGPT= Serum Glutamic Pyruvic Transaminase, TSH= Thyroid Stimulating Hormone

4.1.4 Analysis of anti-Diabetic therapy:

In table 7, analyzing the anti-diabetic therapy taken by the participants, 47 (29.70%) participants have to take injection insulin and 111 (70.30%) don't take Insulin. Among insulin users only 2 (1.3%) are solely taking only Insulin to control diabetes. Of the rest 45 insulin users, 13 (8.2%) take Insulin with OAD and rest 32 (20.2%) take Insulin, Oral anti-diabetic drug (OAD) & other measure. 145 participants, who are taking OAD, 56 (35.4%) take Metformin, 11(7.0%) take Sulfonylurea, 1(0.6%) take DPP(Dipeptidyl peptidase)-4 Inhibitors, 3(1.90%)take SGLT(Sodium-Glucose Transport protein)-2 inhibitors and the rest take combination from above. Among the patients who are taking combination of OAD with Metformin, 58 (37.2%) take one OAD with Metformin, 24 (15%) take two OAD with Metformin and 1 (0.6%) take three OAD with Metformin respectively. Regarding the Insulin injection sites 23 (49%) participants take injection in the skin of abdomen, 5 (10.7%) in Thigh, 16 (34%) in both abdomen and thigh, 2 (4.2%) in arm and 1 (2.15) in all sites.46.8% Insulin users suffered from hypoglycemic attack due to extracorporeal Insulin and 23.4% required hospitalization due to extracorporeal Insulin.

Table 7: Anti Diabetic therapy (n=158)

Variable	Category	n	%
Therapy regarding insulin use	Insulin user	47	29.70
	Insulin non user	111	70.30
Insulin user	Only Insulin	02	1.3
	Insulin with OAD	13	8.2
	Insulin,OAD & other measurement	32	20.2
Oral anti-diabetic drug	Metformin	56	35.4
	Sulfonylurea	11	7.0
	DPP-4 inhibitors	1	.6
	SGLT-2 inhibitors	3	1.8
	Other single OAD	2	1.2
	Metformin with single OAD	58	37.2
	Metformin with two OAD	24	15
	Metformin with three OAD	1	.6
	Other 2 OAD	1	.6
	Other 3 OAD	1	.6
Insulin injection sites used	Abdomen	23	49.0
	Thigh	5	10.7
	Both Abdomen& thigh	16	34.0
	Arm	2	4.2
	All	1	2.1
H/O hypoglycemic attack from extracorporeal Insulin	No	25	53.2
	Yes	22	46.8
Require hospitalization for Hypoglycemic attack due to Insulin	Yes	11	23.4
	No	36	76.6

Note: OAD= Oral Anti-diabetic Drug, DPP = Dipeptidyl peptidase, SGLT = Sodium-Glucose Transport protein

4.1.5 Self-care behavior analysis of T2DM patients:

For a diabetic patient, diabetic self-care behavior is a very important part of both for daily well-being and also for the good glycemic control. Table 8 shows that, out of total 158 T2DM participants 13.3% don't do any daily exercises whether rest do daily exercises which varies from minimum 30 minutes brisk walking up to 90minutes brisk walking. 60.1% regularly test blood glucose and 39.1% don't. Blood sugar test frequency is for 7.6% once a day, 4.4% two or more times a day, 22.2% Once/Twice in a week, 44.9% once in a month and rest 20.9% are rarely/never. Among these individuals only 21.5% keep the capillary blood glucose (CBG) test record and other 78.5% don't. 7.6% did urine for sugar or ketones whether 92.4% didn't. Regarding regular eye checkup 91.1% goes for eye checkup on need, 3.8% occasionally and 5.1% don't checkup eye regularly. On the basis of regular dental checkup, 78.5% go for dental checkup if needed, 4.4% goes for monthly dental checkup, and 1.3% yearly and 15.8% never went for dental checkup. 50% participants checked their Cholesterol and Triglycerides where 50% didn't. From 158 sample only 49(41%) did HbA1c test.

Table 8: Diabetic self-care behavior (n=158)

Variable	Category	n	%
Performing physical exercise everyday:	No	21	13.3
	Heavy(brisk walk>90mins)	7	4.4
	Moderate(brisk walk60-90mins)	31	19.6
	Mild (brisk walk 30-59mins)	56	35.4
	Sedentary(brisk walk<30mins)	43	27.2
Regularly blood sugar test?	Yes	95	60.1
	No	63	39.9
Blood sugar is test frequency:	Once a day	12	7.6
	2 or more times/day	7	4.4
	Once/Twice a week	35	22.2
	Once in a month	71	44.9
	Rarely/Never	33	20.9
Record keeping of CBG	Yes	34	21.5
	No	124	78.5
Test your urine for sugar or ketones?	Yes	12	7.6
	No	146	92.4
Eyes checking by a doctor :	Occasionally	6	3.8
	On need	144	91.1
	No	8	5.1
Checking feet at home?	Daily	16	10.1
	Weekly	11	7.0
	Never	131	82.9
Dental checkup?	Never	25	15.8
	Monthly	7	4.4
	Yearly	2	1.3
	On need	124	78.5
Have you had your cholesterol or triglycerides checked?	Yes	79	50.0
	No	79	50.0
HbA1c test done:	Yes	49	31.0
	No	109	69.0

Note: CBG= capillary Blood Glucose

4.2 Baseline comparison between Male & Female:

Baseline comparison between male and female T2DM patients regarding their physical characteristics, economic status and chronic complications are being discussed below.

4.2.1 Baseline comparison between Male & Female regarding Socio-demographic status and chronic complications& associated factors of T2DM:

Table 9 shows student's t-Test result of the baseline comparison between male & female regarding socio-demographic status and chronic complications of T2DM and associated factors with related biochemical laboratory values including minimum value, maximum value and mean with standard deviation. Here height and weight are higher in male ($p<.05$) where BMI is significantly higher in female ($p<.05$). Monthly income (MI) also shows higher in male ($p<.05$) and duration of Hypertension is higher in female ($p<.05$).

Table 9: Baseline characteristics between Male & Female T2DM individual (n=158): t-Test

Variable	Male				Female				
	n	Min	Max	Mean ± SD	n	Min	Max	Mean ± SD	*p*
Age (*year*)	72	28	83	53.07±12.85	86	30	74	49.60±11.45	.075
SBP *(mm of Hg)*	72	100	170	127.98±15.26	86	100	210	131.92±20.26	.177
DBP*(mm of Hg)*	72	60	100	82.5±8.39	86	40	130	81.10±12.33	.416
Height*(cm)*	72	137.16	187.9	167.85±8.47	86	140	172	156.02±5.78	**.000**
Weight *(kg)*	72	55	95	71.35±9.40	86	43	110	66.85±12.80	**.014**
BMI *(Kg/m^2)*	72	19.8	32.3	25.31±2.86	86	17.9	44.3	27.34±4.85	**.001**
Diabetic duration *(years)*	72	0.5	30	7.34±7.28	86	0.5	32	6.73±6.60	.581
FM *(in number)*	72	3	8	4.89±1.29	86	2	5	5.15±1.61	.268
Income*(Thousand BDT/month)*	72	0	60	21.68±17.04	86	0	50	3.37±8.97	**.000**
ITD*(years)*	22	0.5	15	3.57±3.90	25	0.5	20	5.18±4.79	.218
Eye problems *(years)*	30	1	17	5.52±4.60	33	0.5	40	7.57±8.78	.257
Ear problems *(years)*	4	0.5	20	6.75±9.03	1	1	1	1	.609
IHD *(years)*	13	0.5	10	3.50±2.61	20	0.5	6	2.27±1.56	.102
Hypertension *(years)*	38	1	10	3.9474±2.59	48	1	40	6.13±5.98	**.026**
Dyslipidemia *(years)*	30	0.5	10	3.27±2.72	40	0.5	10	3.35±2.41	.887
S. Cholesterol *(mg/dL)*	10	122	266	192.60±42.09	25	102	315	212.32±46.39	.253
Triglycerides *(mg/dL)*	10	159	410	229.4±81.75	25	134	484	245.56±97.09	.646
Lungs problems *(years)*	8	0.5	42	7.06±14.24	5	2	15	7.80±5.07	.914
BP *(years)*	24	0.5	8	3.08±2.42	33	0.5	6	2.96±2.33	.859
CVD*(years)*	1		6	6	3	0.5	6	2.83±2.84	.437
TGP *(years)*	24	2	30	7.92±7.26	33	0.5	50	7.02±9.57	.627
FLP *(years)*	20	1	5	2.31±1.37	28	0.5	10	2.82±2.06	.348
GIT problems *(years)*	13	1	6	3.15±1.67	25	0.5	6	2.63±1.55	.344
SP *(years)*	9	0.5	5	1.83±1.63	6	0.5	3	1.50±1.18	.676
Kidney problems *(years)*	3	2	5	3.00±1.73	10	0.5	6	2.10±1.88	.477
Creatinine level *(mg/dL)*	6	0.7	1.4	1.05±.30	16	0.6	2.8	1.42±.65	.086
Liver disease *(years)*	2	2	2	2.0±.00	7	0.5	2	1.21±.56	.104
SGPT level *(U/lit)*	2	38	80	59±29.69	11	26	87	47.36±19.92	.486
PP *(years)*	1	5	5	5	1	0.5	0.5	.50	
AP *(years)*	7	1	6	3.57±1.81	7	1	7	2.33±1.67	.149
BJP *(years)*	11	0.5	7	2.67±1.86	23	0.5	7	2.99±1.97	.691

Note: Min=Minimum, Max=Maximum**,** SBP=Systolic Blood Pressure, DBP= Diastolic Blood Pressure, Kg= kilogram, BMI= Body Mass Index, FM= Family member, MI= Monthly Income, ITD= Insulin Taking Duration, IHD= Ischemic Heart Disease, BP= Burning problems, CVD= Cerebrovascular Disease, TGP= Teeth/Gum problem, FLP= Foot/ Leg Problem, SP= Sexual Problem, PP= Psychological Problem, AP= Allergic Problem, BJP= Bones & Joints Problem, GIT= Gastrointestinal Tract, SGPT= Serum Glutamic Pyruvic Transaminase.

4.2.2 Analysis of type of complications and associated factors of T2DM:

T2DM leads a patient to some chronic complications, where these are associated with factor like hypertension and Dyslipidemia. Table 10.1 shows the type of complications and associated factors of T2DM where there are three variables; Microvascular complications, Macrovascular complications and T2DM Associated factors. Microvascular complications (Diabetic retinopathy / Eye problems 38.60% ,Diabetic Nephropathy/ Kidney problems 8.22% and rest Diabetic Neuropathy symptoms which includes Paraesthesia/Burning problems 36%, Periodontitis/Teeth/Gum problems 36.70%, GIT problems like IBS, Constipation 24.05% , Sexual function problem like Erectile dysfunction, Loss of libido, Frigidity 9.50% and 1.26% have Psychological problems like Anxiety disorders, Depression), Macrovascular complications (20.88% IHD, 2.53% CVD and no Diabetic foot found) are found. T2DM associated factors are seen 54.43% have Hypertension, 44.90% have Dyslipidemia, both HTN and Dyslipidemia in 37.97% individual and only 1.3% had none of them.

Table 10.1: Type of complications and associated factors of T2DM (n=158)

Variable	Category	Symptoms/Problems	n	%
Microvascular complications	Diabetic Retinopathy symptoms	Eye problems	61	38.60
	Diabetic Neuropathy symptoms	1. Paraesthesia/Burning	57	36.07
		2. Periodontitis/Teeth and Gum problems	58	36.70
		3. GIT problems (IBS, Constipation)	38	24.05
		4. Sexual function problems (Erectile dysfunction, Loss of libido, Frigidity)	15	9.50
		5. Psychological problems (Anxiety, Depression)	02	1.26
	Diabetic Nephropathy	Kidney problems	13	8.22
Macrovascular complications	IHD		33	20.88
	CVD		04	2.53
	Diabetic foot		00	0.00
Associated factor	1. Hypertension		86	54.40
	2. Dyslipidemia		70	44.30
	3. No HTN or Dyslipidemia		02	1.3
	4. Both HTN & Dyslipidemia		60	37.97

Note: GIT= Gastrointestinal Tract, IHD= Ischemic Heart Disease, CVD= Cerebrovascular Disease

4.2.3 Analysis of number of T2DM complications and associated factors of T2DM:

Table 10.2 shows number of complications and associated factors of T2DM where 26.58% have no complications or associated factor, 15.19% have more than five, 5.70% have five, 15.19% have four, 14.55% have three, 10.76% have two and 12.03% have one complication or associated factor of T2DM

Table 10.2: Number of T2DM complications and T2DM associated factors (HTN, Dyslipidaemia) (n=158)

Variable	n	%
One	19	12.03
Two	17	10.76
Three	23	14.55
Four	24	15.19
Five	09	5.70
More than five	24	15.19
No complication or associated factor	42	26.58

4.2.4 Comparison between male and female regarding number of complications and associated factors of T2DM:

This study has found out some differences between male and female regarding number of complications and associated factors of T2DM. In table 10.3, in case of female there is 30.23% having no complications or T2DM associated factors whether 22.22% male don't have any of them. Almost 19% female and 11.11% male shows have more than five complications or associated factors respectively. Number of one, three and four complications or associated factors is more in male than female, where number of two and five complication or associated factor is higher in female.

Table 10.3: Comparison between male and female regarding number of complications and associated factors of T2DM (n=158)

Variable (Number of complications and associated factor)	Frequency with %			
	Male (n 72)	%	Female(n 86)	%
One	12	16.67	07	8.1
Two	07	09.72	10	11.62
Three	13	18.05	10	11.62
Four	12	16.67	12	13.95
Five	04	05.55	05	5.81
More than five	08	11.11	16	18.60
No	16	22.22	26	30.23

4.2.5 Male-Female comparison in correlation between chronic complications and associated factors:

Table 11 shows the Male-Female comparison on the basis of correlation between chronic complications and associated factors. This table shows highly significant difference between male and female where there is strongly positive correlation between HTN and Exercise (Female > Male), strongly positive correlation between Dyslipidemia and Exercise (Female > Male), strongly positive correlation between Dyslipidemia and HTN (Female > Male), strongly positive correlation between Teeth/Gum problems and HTN (Female > Male).

It also shows Positive correlation between Bones and Joints pain and HTN (Female > Male),strongly positive correlation between IHD and HTN (Female > Male), positive correlation between Burning problem and Dyslipidemia(Female > Male),strongly positive correlation between Teeth/Gum problem and Dyslipidemia (Female > Male),strongly positive correlation between GIT problem and Dyslipidemia (Female > Male),strongly positive correlation between IHD and Dyslipidemia (Female > Male),strongly positive correlation between Teeth/Gum problem and Burning (Male > Female),strongly positive correlation between GIT problem and Burning (Female < Male),strongly positive correlation between Allergic problem and Burning in Female, strongly positive correlation between Bones and Joints problem & Burning (Female > Male), positive correlation between IHD and Burning in female and negative correlation in male, strongly positive correlation between IHD and Teeth/Gum problem (Female > Male),strongly positive correlation between GIT and Teeth/Gum problem (Female > Male),strongly positive correlation between Sexual function problem and Teeth/Gum problem (Female > Male).

Strongly positive correlation between Allergy and Teeth/Gum problem in Female is shown with, strongly positive correlation between Bones and Joints problem and Teeth/Gum problem (Female < Male),strongly positive correlation between IHD and GIT problem in Female ,strongly negative correlation between Daily sunlight exposure and Teeth/Gum problems (Female > Male),strongly positive correlation between Sexual function problem and GIT problem (Female > Male),strongly positive correlation between Allergy problem and GIT problem (Female > Male),strongly positive correlation between Bones and Joints pain & GIT problem (Female > Male),strongly positive correlation between IHD and GIT problem in

Female, strongly positive correlation between Allergy and Sexual Function problem in Female and strongly positive correlation between Bones and Joints pain and IHD in Female.

Table 11: Male-Female comparison in correlation between chronic complications and associated factors (n=158)

VAR	EX		HTN		DLP		BUP		TGP		GITP		SP		AP		BJP		SLE		IHD	
	M	F	M	F	M	F	M	F	M	F	M	F	M	F	M	F	M	F	M	F	M	F
EX	-	-	.218	.364**	.153	.342**	-.107	.011	.009	.077	.011	.141	-.038	.124	-.071	-.110	.135	.121	.106	-.171	.142	.165
HTN	.218	.364**	-	-	.517**	.586**	.197	.199	.281*	.299**	.299*	.151	-.147	.066	-.065	-.002	.050	.215*	-.113	-.183	.227	.491**
DLP	.153	.342**	.517**	.586**	-	-	.120	.247*	.212	.296**	.189	.325**	-.149	.119	.103	.002	.227	.166	.131	-.105	.409**	.538**
BUP	-.107	.011	.197	.199	.120	.247*	-	-	.660**	.642**	.511**	.445**	.356**	.171	.265*	.434**	.316**	.330**	-.099	-.100	-.026	.235*
TGP	.009	.077	.281*	.299**	.212	.296**	.660**	.642**	-	-	.492**	.499**	.077	.363**	.155	.288**	.378**	.330**	-.010	-.348**	.037	.353**
GITP	.011	.141	.299*	.151	.189	.325**	.511**	.445**	.492**	.499**	-	-	.368**	.336**	.333**	.458**	.371**	.342**	-.134	-.151	.155	.288**
SP	-.038	.124	-.147	.066	-.149	.119	.356**	.171	.077	.363**	.368**	.336**	-	-	.159	.577**	.169	.045	-.133	-.066	-.177	-.039
AP	-.071	-.110	-.065	-.002	.103	.002	.265*	.434**	.155	.288**	.333**	.458**	.159	.577**	-	-	.105	.250*	-.076	.002	.333**	-.041
BJP	.135	.121	.050	.215*	.227	.166	.316**	.330**	.378**	.330**	.371**	.342**	.169	.045	.105	.250*	-	-	-.063	-.161	.081	.325**
SLE	.106	-.171	-.113	-.183	.131	-.105	-.099	-.100	-.010	-.348**	-.134	-.151	-.133	-.066	-.076	.002	-.063	-.161	-	-	-.043	-.206
IHD	.142	.165	.227	.491**	.409**	.538**	-.026	.235*	.037	.353**	.155	.288**	-.177	-.039	.333**	-.041	.081	.325**	-.043	-.206	-	

N.B: VAR= Variable, EX= Daily exercise, HTN= Hypertension, DLP= Dyslipidemia, BUP= Burning problems, TGP= Teeth/Gum Problems, GITP= Gastrointestinal Tract problems, SP= Sexual problems, AP= Allergic Problems, BJP= Bones & Joints Problems, SLE= Sunlight Exposure daily, IHD= Ischemic Heart Diseases

* Significant correlation

** Strongly correlated

4.3 Analysis of type of complications and associated factors of T2DM:

Chi square test of T2DM complications and associated factors (HTN, Dyslipidemia) shows us the comparison among complications and associated factors where Insulin user-non user, Daily sunlight exposure and daily exercise were the dependent variables.

4.3.1 Comparison among complications and associated factors (Independent variable: Daily exercise):

χ2-test result on the basis of comparison among complications and associated factors where independent variable is daily exercise is shown in table 14 which shows significant difference in Hypertension (p<.000) and Dyslipidemia (p<.003).

Table 12: Prevalence of complications between daily exercise and without daily exercise in T2DM patients (n=158): χ2-test

Variable	Category	Total(n)	With DE (%)	Without DE (%)	*p*
Hypertension	Yes	86	95.4	4.6	**.000**
	No	72	77.8	22.2	
IHD	Yes	33	90.5	9.5	.169
	No	125	77.4	22.6	
Dyslipidemia	Yes	70	95.7	4.3	.003
	No	88	79.5	20.5	
Burning problem	Yes	57	84.2	15.8	.487
	No	101	88.1	11.9	
Teeth/Gum problem	Yes	57	87.7	12.3	.779
	No	101	86.1	13.9	
Feet/Leg cramp problem	Yes	48	87.50	12.50	.768
	No	110	86.4	13.6	
GIT problem	Yes	38	89.5	10.5	.553
	No	120	85.0	15.0	
Sexual Function problem	Yes	15	93.3	6.7	.427
	No	143	86.0	14.0	
Kidney problem	Yes	13	100	0.0	.141
	No	145	85.5	14.5	
Liver problem	Yes	09	100	0.0	.226
	No	149	85.9	14.1	
Thyroid problem	Yes	14	100	0.0	.125
	No	144	85.4	14.6	
Allergic problem	Yes	19	78.9	21.1	.288
	No	139	87.8	12.2	
Bones & Joints problem	Yes	34	91.2	8.8	.386
	No	124	85.5	14.5	
Anxiety	Yes	121	88.4	11.6	.249
	No	37	81.1	18.9	
Sex	Male	72	90.3	9.7	.249
	Female	86	83.7	16.3	

Note: DE= Daily Exercise, IHD= Ischemic Heart Disease, GIT= Gastrointestinal Tract

4.3.2 Comparison among Complications and associated factors (Independent variable: Insulin user-non user):

$\chi 2$-test results (Insulin user-non user was the independent variable) shows in table 13.1 where Hypertension (p<.010), IHD (p<.008), Burning problem (p<.011), GIT problem (p<.002), Kidney problem (p<.047) show significant difference in Insulin users and Non-users.

Table 13.1: Prevalence of complications between Insulin user and non-user in T2DM patients (n=158) : $\chi 2$-test

Variable	Category	Total	IU (%)	INU (%)	*p*
Hypertension	Yes	86	38.4	61.6	.010
	No	72	19.4	80.6	
IHD	Yes	33	48.5	51.5	.008
	No	125	24.8	75.2	
Burning	Yes	57	42.1	57.9	.011
	No	101	22.8	77.2	
Teeth/Gum	Yes	57	40.4	59.6	.028
	No	101	23.8	76.2	
Feet/Leg cramp	Yes	48	39.6	60.4	.024
	No	111	25.2	74.8	
GIT	Yes	38	50.0	50.0	.002
	No	120	24.2	75.8	
Kidney	Yes	13	53.9	46.1	.047
	No	145	27.6	72.4	

Note: IU= Insulin User, INU= Insulin Non-user, IHD= Ischemic Disease, GIT= Gastrointestinal Tract

- Selection criteria: p< 0.05

On the basis of Chi square test of comparison among Complications and associated factors (where dependent variable was Insulin user-non user), the multiple linear regressions were done and the comparison between Insulin user and Insulin non user was done by the using following calculation (Here predictor value of insulin user is, e=1) were shown in table 13.2.which are shown below. Insulin non user predictor value = e^x (x= value of β coefficient)

Table 13.2: Risk of complications among T2DM patients by category of Insulin user among total participants (n=158)

Variable	β (95% CI)	Insulin user	Insulin non-user	*p*
HTN	.088(-.077~.238)	1	1.09	.312
Teeth/gum problem	.091(-.310~.137)	1	1.09	.444
Feet/leg problem	.107(-.093~.317)	1	1.11	.282
GIT problem	.164(-.019~.370)	1	1.18	.077
IHD	.118(-.055~.320)	1	1.13	.166
Burning problem	.083(-.126~.284)	1	1.09	.447
Kidney problem	.088(-.116~.409)	1	1.09	.272

Note: HTN= Hypertension, GIT= Gastrointestinal Tract, IHD= Ischemic Heart Disease

HTN: Predictor value for Insulin non user 1.09 means, 1.09-1= 0.09 0r 9% more in Insulin non user than Insulin user.

Teeth/Gum problems: Predictor value for Insulin non user 1.09 means, 1.09-1= 0.09 0r 9% more in Insulin non user than Insulin user.

Feet/Leg problems: Predictor value for Insulin non user 1.11 means, 1.11-1= 0.11 0r 11% more in Insulin non user than Insulin user.

GIT problems: Predictor value for Insulin non user 1.18 means, 1.18-1= 0.18 0r 18% more in Insulin non user than Insulin user.

IHD: Predictor value for Insulin non user 1.13 means, 1.13-1= 0.13 0r 13% more in Insulin non user than Insulin user.

Burning problems: Predictor value for Insulin non user 1.09 means, 1.09-1= 0.09 0r 9% more in Insulin non user than Insulin user.

Kidney problems: Predictor value for Insulin non user 1.09 means, 1.09-1= 0.09 0r 9% more in Insulin non user than Insulin user.

Multiple linear regressions (independent variable insulin user and Insulin non user) through several models show diabetic neuropathy related complications or symptoms (burning problems are taken as common variable) had significant p value ($p<0.05$). On the basis of p value of independent factor burning problem, the comparison between Insulin user and Insulin non user was done by the using following calculation (Here predictor value of insulin user is, e=1) were shown in table 13.3.

Insulin non user predictor value = e^x (x= value of β coefficient)

Table 13.3: Risk of complications among T2DM patients by category of Insulin user among total participants

Model no.	β (95% CI)	Insulin user	Insulin non-user	*p*
Model 1	.159(.003~.300)	1	1.17	.046
Model 2	.157(-.047~.345)	1	1.17	.136
Model 3	.178 (.023~.316)	1	1.19	.023
Model 4	.167 (.010~.308)	1	1.18	.037

Note: HTN= Hypertension, IHD= Ischemic Heart Disease, GIT= gastrointestinal tract

Table 13.3 shows that the predictor value for Insulin non user in:

- **Model 1:** Predictor value for Insulin non user 1.17 means, 1.17-1= 0.17 0r 17% more burning problems in Insulin non user than Insulin user, adjusted for Burning problems, HTN and IHD
- **Model 2:** Predictor value for Insulin non user 1.17 means, 1.17-1= 0.17 0r 17% more burning problems in Insulin non user than Insulin user, adjusted for Burning problems, HTN and Teeth/Gum problems
- **Model 3:** Predictor value for Insulin non user 1.19 means, 1.19-1= 0.19 0r 19% more burning problems in Insulin non user than Insulin user, adjusted for Burning problems and IHD
- **Model 4:** Predictor value for Insulin non user 1.18 means, 1.18-1= 0.18 0r 18% more burning problems in Insulin non user than Insulin user, adjusted for Burning problems and HTN

4.3.3 Comparison among complications and associated factors (Dependent variable: Daily sunlight Exposure):

In table 14.1, the result of $\chi 2$-test are shown on the basis of comparison among complications and associated factors where the independent variable is daily sunlight exposure. Here sex ($p<.000$), teeth/gum problem ($p<.017$), Feet/Leg cramp ($p<.008$), GIT problem ($p<.045$) shows significant differences between factors.

Table 14.1: Prevalence of complications between daily sunlight exposure or not in T2DM patients: $\chi 2$-test

Variable	Category	Total (n)	DSLE, Yes (%)	DSLE, No (%)	*p*
Sex	Male	72	80.6	19.4	**.000**
	Female	86	45.3	54.7	
Hypertension	Yes	86	54.6	45.4	.057
	No	72	69.4	30.6	
Teeth/Gum problem	Yes	57	49.1	50.9	**.017**
	No	101	68.3	31.7	
Feet/Leg cramp	Yes	48	45.8	50.9	**.008**
	No	110	68.2	31.8	
GIT problem	Yes	38	47.4	52.6	**.045**
	No	120	65.8	34.2	
Bones & Joints problem	Yes	34	47.0	53.0	.053
	No	124	65.3	34.7	

Note: DSLE=Daily Sunlight Exposure, GIT= Gastrointestinal Tract

- Selection criteria: $p < 0.06$
-

On the basis of comparison among Complications and associated factors where dependent variable was Daily Sunlight Exposure and independent factor was Sex, the multiple linear regressions were done through different models adjusted for different chronic complications and risk factors associated with T2DM. On the basis of p value of independent factor Male sex, the comparison between Male and Female was done by the using following calculation (Here predictor value of Male is, e=1) were shown in table 14.2.

Female predictor value = e^x (x= value of β coefficient)

Table 14.2: Risk of complications among T2DM patients by category of daily sunlight exposure among total participants

Model no.	β (95% CI)	Male	Female	*p*
Model 1	.341 (.190~.477)	1	1.40	**.000**
Model 2	.345 (.194~.480)	1	1.41	**.000**
Model 3	.345 (.194~.480)	1	1.41	**.000**

Note: HTN= Hypertension, GIT= Gastrointestinal Tract

Table 14.2 shows that the predictor value for Female in

Model 1: Predictor value for Female 1.40 means, 1.40-1= 0.40 0r 40% more problems in Female than Male, adjusted for Sex, HTN, Teeth/gum problem, Feet/leg problem, GIT problem, Bones & Joints problem.

Model 2: Predictor value for Female 1.41 means, 1.41-1= 0.41 0r 41% more problems in Female than Male, adjusted for Sex, HTN, Teeth/gum problem, Feet/leg problem, GIT problem

Model 3: Predictor value for Female 1.41 means, 1.41-1= 0.41 0r 41% more problems in Female than Male, adjusted for Sex, Teeth/gum problem, Feet/leg problem, GIT problem


Discussion

Chapter V: Discussion

T2DM is a global burden. The main problem with T2DM is hyperglycemia, which ultimately lead to various Microvascular and Macrovascular complications, which are also associated with some factors. The study focus was to find out the prevalence of T2DM complications in Chattogram city, Bangladesh. The author aimed at to find out the complications and associated factors of T2DM in broader aspect, and also enlighten the larger population regarding these, find out the important risk factor behind the mechanism of complications. Thus give better lifestyle guideline for the T2DM patients.

In this study 158 individuals' data were taken where the highest (55.7%) participants are from author's personal chamber and lowest (13.9%) from Chattogram Diabetic General Hospital (CDGH) from October 2020 to October 2021 by using questionnaire with written consent of the participants . From these 158 individuals 54.4% are female and 45.6% are male. 62.1% participants are from urban and 1.8% is living in overseas. 84.2% participants are married, 3.2% are single, 1.9% is divorced and 10.8% are widowed. 50% participants don't do any job, 21.5% are job holder, 17.7% are businessmen, 2.8% are farmers and rest 5.1% is retired. On the basis of educational status, 24.6% completed Honors and above, 8.9% illiterate, 20.9% completed primary, 20.3% completed rest SSC and rest 25.3% completed HSC. The proportion of living in nuclear family is higher (51.9%) than joint family (48.1%). According to the religious status 94.4% participants were Muslims, 4.4% were Hindus, 0.6% was Christian and 0.6% was Buddhist.

Regarding lifestyle and behavior, 75.3% had never smoked and 20.3% were former and 4.4% were current smokers. 95% participants never consumed alcohol, whether 2.5% were former and 2.5% were occasional alcohol consumer. 86.7% participants do daily exercise and only 13.3% individuals don't. 79.7% participants follow diet chart either by diabetologist, or internet or self-implicated and only 20.3% don't. 76.6% participants have anxiety and the 23.4% haven't any, 62.7% don't have sound sleep. From these 158 participants, 38.6% don't go for daily sunlight exposure and 61.4% have daily sunlight exposure which varies from few hours to 6-8 hours. 53.1% participants were neither happy nor unhappy, 16.5% were unhappy, 4.4% were very

unhappy, 24.1 % were happy and only 1.9% were very happy. The systolic blood pressure was ranging from 100 to 210mm (Hg) averaging 130mm(Hg) and the diastolic BP was ranging from 40 to 130 mm (Hg) which indicates Hypertension is a very important associated factor for T2DM. The result also reflects that 54.43% participants have HTN and 8.22% patient have Kidney problem. As HTN and kidney problems are closely associated (Elaine *et al.,* 2019), this finding is also coincides with the earlier study in Ethiopia where HTN and renal disease 35.4% (Gizaw *et al.,* 2019). The BMI of the participants ranges from 18-44 averaging 26.41 which indicates the relationship between BMI and T2DM complications in study shows elevated BMI is associated with a progressively increasing the risk of complications from T2DM. Women having BMI ≥40 have high risk of insulin dependencies two times more than for women with 25 ≤ BMI. Same pattern was also observed in risk of IHD, CVD and in Diabetic Nephropathy (Natallia *et al.,* 2015). Only 22.1% participants provided their total Serum Cholesterol and Triglycerides values averaging 207 mg/dL with range from 102-315mg/dL and 241 mg/dL ranging from 134-484 mg/dL respectively, showing higher value than normal. This dyslipidemia is an important contributing factor for T2DM complications. It is one of the major risk factors for IHD in diabetes mellitus. Here in case of Dyslipidemia there are high plasma triglyceride concentration with low HDL cholesterol concentration and increased concentration of small dense LDL-cholesterol particles which ultimately leads to atheroma formation, leading to increase the chance of cardiovascular event (Arshag, 2009*)*. This dyslipidemia also contributes to Cerebrovascular disease *(*Boyle, 2007) 13.9% participants gave their serum creatinine value ranging from 1-3 mg/dL with an average of 1.32 mg/dL. Increase creatinine is an important biochemical marker to assess the Diabetic Nephropathy ultimately leading to chronic Kidney disease (Ron and Jialal , 2021). A number of 13 participants gave SGPT laboratory value averaging 49 Unit/ Lt, ranging from 13-87 Unit/Lt which indicates Fatty Liver disease. Around 84% participants have family history of T2DM either Father or Mother, or both or siblings and other 1st degree family members which prove a strong association of running T2DM in family. The risk for having T2DM increases approximately by 2-4 times, when father, mother or both have this condition. Studies suggested that the chance of developing T2DM in next generation is higher in diabetic mother than father (Papazafiropoulou *et al.,* 2017).

In this study out of 158 subjects, 29.70% are insulin user, where 2 participants are taking only insulin as only anti diabetic measure and rest 45 use oral anti-diabetic drug and other measures.

It indicates the poor glycemic control in the patients which ultimately leading to Diabetic complications. Chi square test in Table 12 shows Hypertension (p<.01), CVD (p<.008), Burning problem (p<.011), GIT problem (p<.002), Kidney problem (p<.047) shows significant difference in Insulin users and non-users. Which inform us the people who have already developed chronic complications of T2DM have to take Insulin. Linear regression analysis of the correlations regarding Insulin user adjusted for multiple chronic complications and associated factor of T2DM also shows significant *p* values for Microvascular and Macrovascular complications in Model 1, Model 2, Model 3 and Model 4 (Table 13.2).

The study shows, using Oral anti diabetic drug 35.4% are taking Metformin, 7.0% Sulfonylurea, 0.6% DPP-4 Inhibitors, 1.90% SGLT-2 inhibitors and the rest 54% take combination of OADs either with Metformin or other, which collaborates with a study in India showing 56% uses combination of OAD (Lahiry *et al.,* 2017). Among 158 patients 29.70% are insulin user combined with other OAD and 1.2% participants are taking only insulin. A study in Dhaka Medical College hospital in 2016 which sowed 41% were prescribed Biguanides alone , combined OAD were 31.4% and 37.1% were prescribed Insulin (Zuhayer *et al.,* 2016) which has some similarities with current study. Near 46% Insulin users suffered from hypoglycemic attack due to extracorporeal Insulin and 23.4% required hospitalization due to extracorporeal Insulin.

Analyzing the diabetic self-care behavior, our 86.7% participants do a daily exercise which varies from minimum 30 minutes brisk walking up to 90 minutes brisk walking and 13.3% don't. Of these 158 individuals, 38.6% don't go for daily sunlight exposure and 61.4% have daily sunlight exposure which varies from few hours to 6-8 hours. The Chi-square test shows sex (p<.000), teeth/gum problem (p<.017), Feet/Leg cramp (p<.008), GIT problem (p<.045) shows significant differences between sunlight exposure or not (Table 13). Linear regression analysis of the correlations regarding Sunlight exposure adjusted for multiple chronic complications and associated factor of T2DM also shows sex is the most important factor in Model 1, Model 2, Model 3 and Model 4. In this study 81% male have daily sunlight exposure where only 45.3% female have. Other studies suggest that daily sunlight exposure less than 5 hours is needed to avoid sunlight associated complications (Lee *et al.,* 2020) and important for Vitamin D deficiency associated Diabetic peripheral neuropathy (Rui *et al.,* 2016) and Diabetic nephropathy

(Hong *et al.,* 2021). Diabetic neuropathy symptom such as teeth/gum problem (Periodontitis) occurs due T2DM (Caused by insulin resistance) also an early sign of fasting Glucose impairment (Islam *et al.,* 2015).

The study shows 60.1% regularly test blood glucose regularly and 39.1% don't. Blood glucose test frequency is for 7.6% once a day, 4.4% two or more times a day, 22.2% Once/Twice in a week, 44.9% once in a month and rest 20.9% are rarely/never. Among these individuals only 21.5% keep the capillary blood glucose (CBG) test record and other 78.5% don't. 7.6% did urine for sugar or ketones whether 92.4% didn't. Regarding regular eye checkup 91.1% goes for eye checkup on need, 3.8% occasionally and 5.1% don't checkup eye regularly. On the basis of regular dental checkup, 78.5% go for dental checkup if needed, 4.4% goes for monthly dental checkup, 1.3% yearly and 15.8% never went for dental checkup. 50% participants checked their Cholesterol and Triglycerides where 50% didn't. From 158 sample only 49 (41%) did HbA1c test done and rest 109 (69%) didn't.

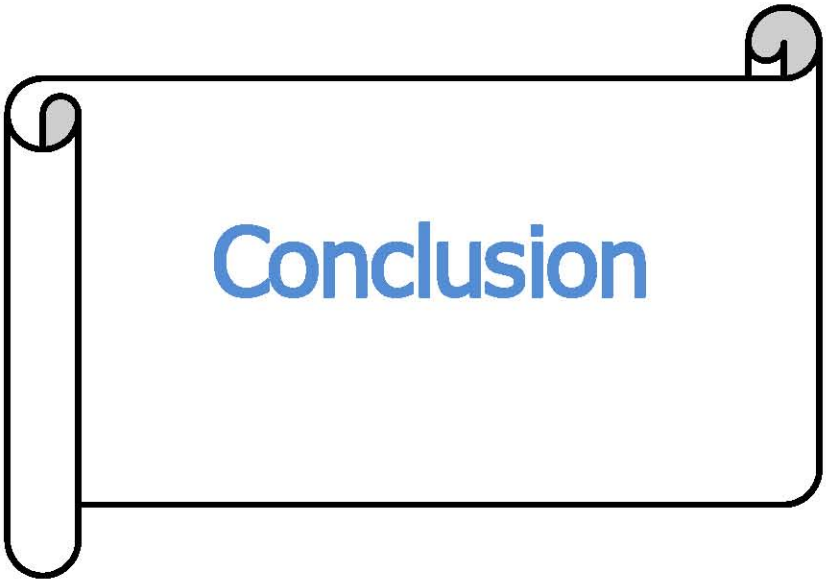
In this study the baseline comparison between male and female regarding socio-demographic status and chronic complications of T2DM and associated factors with related biochemical laboratory values shows BMI($p<.05$) and duration of Hypertension ($p<.05$) are higher in female than male(Table 10).

The T2DM associated complications and associated factors in Table 11.1, Table 11.2 and Table 11.3 also shows that among the participants 38.60% have Diabetic Retinopathy symptoms (Eye problems), 8.22% have Diabetic Nephropathy (Kidney problems) and rest have Diabetic Neuropathy related problems (36.07% have Burning problems, 36.70% have Teeth/Gum problems, 24.05% have GIT problems, 9.50% have Sexual function problem and rest 1.26% have Psychological problems). Regarding Macrovascular complications, 20.88% have IHD and 2.53% have CVD. Also analyzing the T2DM associated factors here shows 54.43% have Hypertension and 44.90% have Dyslipidemia and 37.9% have both HTN and Dyslipidemia. On the context of total number of complications, 26.58% have no complications or associated factor, 15.19% have more than five, 5.70% have five, 15.19% have four, 14.55% have three, 10.76% have two and 12.03% have one complication or associated factor of T2DM. This result shows some similarities with the some studies already been done in different countries all over the world including Bangladesh. In a previous study in Bangladesh showed IHD was found in

30.5% individual, 10.1% CVD case and one or more of the complications were more in female gender (Afsana *et al*., 2019$_b$) which also have similarities with this study. Another study in Ethiopia showed the percentage of complications related to T2DM were CVD 37%, Eye disease 36.4%, HTN and renal disease 35.4% and impotency 23.4% (Gizaw, *et al.,* 2019). Another study in Northern Africa (Tunisia, Egypt & Sudan) from January 1990 to July 2012 showed that, the prevalence of complications are higher in urban area than rural area where the T2DM patients suffered from diabetic retinopathy ranging from 8.1% to 41.5%, Diabetic Nephropathy ranging from 6.7% to 46.3% and Diabetic neuropathy ranges from 21.9% to 60% (Bos and Agyemang *et al.,* 2013). In Ghana, a study was done, which reflects 76.8% of the diabetic patients had some types of complication which includes hypoglycemia (37.9%), peripheral artery disease (3.8%), Diabetic Nephropathy (25.9%) and multiple complications (0.4%). The study also showed that, these complications were prevalent more in females (42.7%) compared to males (34.1%) (Sarpong *et al.,* 2017). A community-based study was carried out in a rural setting in Goa, India in 2011which also showed Diabetic neuropathy (60%), IHD (32.3%) and Diabetic retinopathy (15.4%), Peripheral arterial disease (11.5%) and cerebrovascular disease (6.9%) (Nafisa *et al.,* 2011). This study result shows some similarities with above study results.

In comparison between male and female regarding number of complications and associated factors of T2DM where in case of female there is 30.23% have no complications or associated factors where 22.22% male don't have any. 18.60% female and 11.11% male shows have more than five complications or associated factors respectively. Number of complication or associated factors one (Male 16.7%, Female 8.15%), Two (Male 9.72%, Female 11.62%), three (Male18.05%, Female 11.62%) , four (Male 16.67%, Female 13.95%), Five (male 5.55%, Female 5.81%) , more than Five complications or associated factors (Male 11.11% , female 18.60%), where the study in urban China shows, 33.4% (males: 31.1%; females: 35.1%) suffered from at least one macrovascular complication and 34.7% (males: 28.9%; females: 38.8%) suffered from at least one microvascular complication (Liu et al., 2010). The overall prevalence of complications among female subjects was significantly higher than in male subjects ($\chi 2 = 9.75$, $p = 0.002$), mainly in neuropathy ($p < 0.001$) and eye problems ($p < 0.013$) (Liu *et al.,* 2010) and also in Ghana (Sarpong *et al.,* 2017). Then the comparison between male and female has been done, which also shows the prevalence is greater in female than male. On the basis of comparison Chi-square test was done for several dependent variables Daily exercise,

Insulin user-nonuser and Daily sunlight exposure respectively. The result shows significant values ($p<0.05$) for some independent variables for separate dependent variables. On the basis of p value of risk of complications among T2DM patients by category of different independent variable, multiple linear regressions were done. The multiple linear regressions for insulin user-non-user shows, there the prevalence of Diabetic neuropathy related complications or symptoms HTN, Teeth/gum problem, Feet/leg problem, GIT problem, CVD, Burning problem, Kidney problems are lesser in insulin user than non-users (for burning problems β=.083, 95% CI-.126~.284, p=.447). And when burning problems as the common variable through several models, the multiple linear regression shows increase burning problems in insulin non-user than insulin user (Model 1 shows 17%, Model 2 shows 17%, Model 3 shows 19% and Model 4 shows 18% respectively) with significant p value ($p<0.05$) . The last multiple linear regression for daily sunlight exposure on the basis of sex shows female have more (Model 1 shows 40%, Model 2 shows 41% and Model 3 shows 41% respectively) diabetic neuropathy related complications or symptoms than male($p<0.000$) due to lack of daily sunlight exposure. This indicates daily sunlight exposure (less than 6 hours) is playing an important role to reduce the diabetic neuropathy related complications or symptoms.


Conclusion

Chapter VI: Conclusion

This study revealed that T2DM related complications and associated factors are major burning issues not only for the patient himself, but also for the family. The study aimed at the prevalence of T2DM complications in human in Chattogram where one of the final outcome shows, there is an association between insulin use and Diabetic neuropathy. The patients, who took regular insulin, have less microvascular and macrovascular complications, specifically the T2DM neuropathy symptoms. Another final outcome demonstrates, there is a clear association between Daily sunlight exposure and T2DM Diabetic neuropathy. The study shows, in Chattogram, the patients who have lesser daily sunlight exposure, they have more T2DM neuropathy associated symptoms. As female T2DM patients have less daily sunlight exposure than male, so they have more T2DM neuropathy symptoms and complications than male. So this study suggests for early introduction of Insulin and daily sunlight exposure up to few hours for T2DM patients to reduce the prevalence of T2DM complications.


Strength and Weakness

Chapter VII: Strength and Weakness

The strengths of the present study are, the data have been collected on self by producing a pre structured questionnaire from two hospitals and author's personal chamber where the diabetic patient were physically checked-up and directly interviewed by the author himself. The author assessed the socio-economic status, demographic information, general health characteristics of 158 participants, did the documentation, data entry, data analysis and interpretation.

Strength of this study also includes the size of the sample which has been collected at narrowly defined time period by directly face to face interview. The collected data also associated with instantly available biochemical laboratory value provided by the participants which are related to complications of T2DM.

The limitations of this study are firstly not able to do the neuropathy screening tests and secondly inability to assess all the necessary biochemical laboratory values associated with Type2DM complications and associated factors which could have been more helpful.

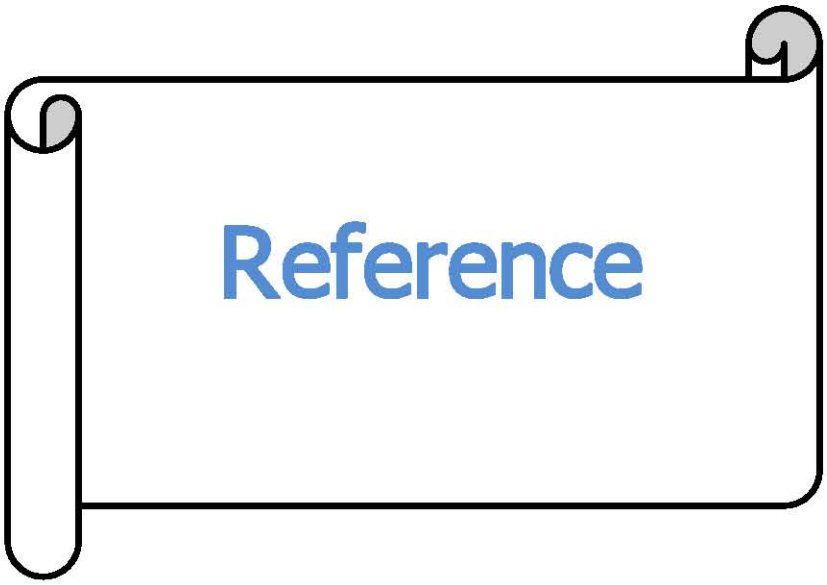
This study may contribute to limited evidence regarding prevalence of complications and associated factor of T2DM by more effective approaches to Diabetic patients regarding diabetic education and proper lifestyle modification, which could ultimately contribute to reduce the burden of Diabetes mellitus associated complications both for patients and also for the society.

The study was based on a cross sectional study which cannot demonstrate properly the cause-effect relationship. It will be necessary to conduct much interventional prospective studies to demonstrate the detailed about the complications and associated factor of T2DM by assessing the necessary bio chemical laboratory value for the prognosis of the complications, thus it can help in improvement of therapy also the lifestyle of a T2DM individual.


Recommendation

Chapter VIII: Recommendation and future perspective

A comprehensive and multi approach study is necessary regarding large sample size, different study locations covering nationwide where all category of the citizen should be included. The essential laboratory biochemical value related to daily sunlight exposure specifically Vitamin D level in blood should be assessed for every T2DM patient to assess the T2DM diabetic complications.


Reference

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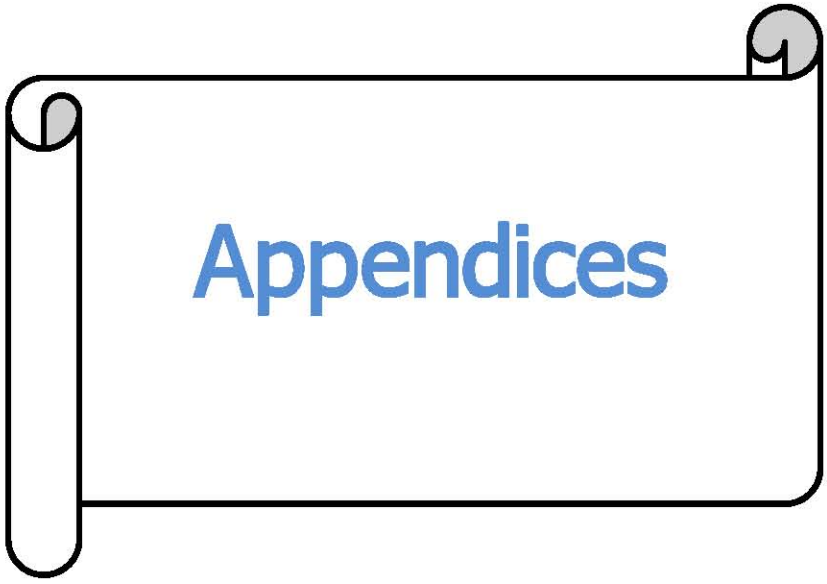
Appendices

Chapter X: Appendices

10.1 Annexes:

Figure 5: Physical examination of the participants

10.2 Questionnaire

Prevalence of Complications of diabetes Mellitus in Chattogram

Place of questionnaire: Chattogram diabetic General Hospital, Personal Chamber & SMCH

Serial no.

A. General Information of the patient:

Date of interview:		1. Patient ID:
2.Name:	3.Age:	4.Sex: i) M ii) F iii) Other
5.Address:		
6. Where do you live in? i) Urban ii) Slum iii) Rural iv) Overseas		
7.Marital status: i) Single ii) Married iii) Divorced iv) Widowed		
8.Occupation: i) Don't do any job ii) Job holder iii) Businessman iv) Farmer v) Retired vi) Other		
9.Educational status: i) Illiterate ii) Primary iii) SSC iv) HSC v) Honors level and above		
10. Type of family? i) Nuclear ii) Joint		
11. Family member:		
12.Religion: i) Muslim ii) Hindu iii) Christian iv) Buddhist v) Other		
13.Attendant (If patient is severely ill):		
14.Monthly income in BDT:		
15.Contact number:		

B. General Examination:

1. Pulse:	2. Blood pressure:	3. Temperature:
4. Respiratory rate	5. Height (In cm):	6. Weight (Kg):
7. Abdominal Circumference (In cm):	8. BMI:	

C. Diabetic history and medication:

1. How long have you been suffering from diabetes (Months/Years)? (Please specify the time period) : i) ____ months ii) _____ years
2. How did you find out diabetic? i) Incidental ii) On suspicion iii) On routine check up
3. Would you please specify the sugar level at the time of Diagnosis? FBS_____ & or 2HAB_____
4. Do you know the type of diabetes do you have? : i)Type1 ii)Type 2 iii) Don't know
5. What type of therapy are you taking for Diabetes Mellitus? i) Oral drug (OHA) ii) Insulin iii) Diet control iv) Insulin with OHA v) Physical exercise vi) None
6. If you take OAD, please mention: i) Biguanides ii) Sulfonylurea iii) DPP-4 inhibitors iv) Alpha-glucosidase inhibitor v) SGLT-2 inhibitors vi) Others:
7. From when you have started taking insulin? i)_____months ii)_____years
8. If you take insulin, who gives the injection? i) Self ii) Other iii) Both
9. Do you check CBG each time before taking insulin? i) Yes ii) No
10. What injection sites are used? : i) Abdomen ii) Thigh iii)Both iv) Arm v)All
11. Do you reuse your syringes?: i) No ii)Yes (How often):
12. Do you have hypoglycemic attack from extracorporeal Insulin? i) No ii) Yes
13. Did you require assistance or hospitalization for it? i) Yes ii) No
14. Do you take any additional nutritional supplements? i) Vitamins ii) Herbal supplements iii) Calcium iv) iron v) Others

D. Information regarding risk factors of a diabetic patient:

1. Family history of Diabetes Mellitus: i) No ii) Father iii)Mother iv) Grandfather v)Grandmother vi)Brother vii)Sister viii)Uncle/Aunt ix)Others :
2. Please mention your smoking status: i) Never smoked ii) Former smoker iii) Current smoker
3. What is your alcohol consumption status: i) Never consumed ii) Former consumer iii) Current consumer iv) Occasional consumer
4. Other drug history: i) No ii) Corticosteroid iii) Oral contraceptive iv) Diuretic v) Hormone Replacement Therapy (HRT) vi) Anti-Hypertensive vii) Lipid lowering viii) Anti ischemic/Platelets ix)Others :
5. Do you have any anxiety? : i) Yes ii) No
6. If yes then mention which environment: i) Working ii) Family Life iii) Social life
7. Do you have sound sleep? : i) Yes ii) No
8. How much sun exposure do you have in a day? i) No exposure ii) 3-5 hours iii) 6-8 hours
9. How much happy are you with your economic solvency?: i) Very unhappy ii) Unhappy iii) Neither happy nor unhappy. iv) Happy v) Very happy.

E. Chronic Complications- Have you ever been told by a doctor of having any problems regarding following systems ?

Problems	**Latest Lab Reports/Latest Examination result/Duration**		
	Duration(in years)	**Type/findings**	**Lab value**
1.Eye			
2.Ear			
3.Heart / Cardiac			
4.Hypertension			
5.Dyslipidemia			
6.Lungs			
7.Burning sensation			
8.Stroke			
9.Teeth/gums			
10.Feet/leg			
11.Skin			
12.Gastrointestinal			
13.Sexual function			
14.Kidneys			
15. Liver			
16. Psychological			
17.Thyroid			
18.Frequent infections			
19.Any surgery regarding DM			
20.Allergy			
21. Bones and joints			
22. Malignancy			
23. Other metabolic problems			

F. Your Diabetes Self Care Behaviors:

1. Do you perform any physical activity? : i) No ii) Heavy: Equivalent to brisk walk of >90 minutes in 24 hours iii) Moderate: Equivalent to brisk walk of 60-90 minutes in 24 hours iv) Mild: Equivalent to brisk walk of 30-59 minutes in 24 hours v) Sedentary: Equivalent to brisk walk of <30 minutes in 24 hours
2. Do you follow any diet plan? i) No ii) By diabetologist iii)Through internet iv) Self-implicated
3. Has your weight changed in the past three months? i)No ii) Didn't check iii) Yes, I've lost_____ kg iv) Yes, I have gained ____ kg
4. How many times do you eat per day? i) Meals _____ ii) Snacks_____
5. From where is your meal ?: i) Home ii) Away
6. How would you describe your appetite? i) Increased ii) Normal iii) Decreased
7. Do you regular test your blood for sugar? i) No ii) Yes at Home/Lab
8. How often do you test? i) Once a day ii) 2 or more times a day iii) Once/Twice a week iv) Once in a month iv) Rarely/Never
9. Do you keep a record? i) Yes ii) No
10. How often do you have HIGH blood sugar? (250 or more) i) Daily ii) Several times a week iii) A few times a month iv) Once in a while v)Rarely or never vi)Don't know
11. How often do you have LOW blood sugar (70 or less)? i) Daily ii) Several times a week iii) A few times a month iv) Once in a while v) Rarely or never vi) Don't know
12. Do you test your urine for sugar or ketones? i) No ii) Yes
13. How often do you have your eyes checked by an eye doctor? : i)Occasionally ii) On need iii)Never
14. How often do you check your feet at home? i) Daily ii)Weekly iii) Never
15. How often do you have a dental checkup? i) Never ii) Monthly iii) Yearly iv) On need
16. Have you had your blood pressure checked? i) Yes ii) No
17. Have you had your cholesterol and triglycerides checked? : i)No ii) Yes
18. Have you had an HbA1c test done? i) No ii) Yes with value(if any)_____%

G. Regarding any blood test during this questionnaire:

If we need to collect blood sample from you regarding your issue, do you agree?

i) Yes ii) No

H. Laboratory examinations:

*Urine *Serum biochemistry *Hormone, *ECG *others

I. Declaration:

I have answered the entire question in the interview sheet and I have full consent about the information given. Best of my knowledge, the information given by me is correct and can be used in research. I have been able to ask any questions I might have, and I understand that I am free to contact the researcher with any question I may have in the future

_____ _____

Signature of interviewee Signature of interviewer

10.3 Brief Biography

Dr. Md. Minhazul Alam passes Secondary School Certificate Examination in 2001 and Higher Secondary Certificate Examination in 2003 respectively under the Chattogram Education Board. Then he completed his MBBS (Bachelor of Medicine and Bachelor of Surgery) from Shaheed Ziaur Rahman Medical College, Bogura under Rajshahi University in 2009. Now he is a candidate for the degree of Masters of Science in Public Health under the department of One Health Institute, Chattogram Veterinary and Animal Sciences University (CVASU). He has immense interest in Public Health and field of Research.