A SURVEY ON THE PREVALENCE OF DIABETES IN TUBERCULOSIS PATIENTS IN NIDCH HOSPITAL, DHAKA

Submitted By

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Department of Pharmacy

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A SURVEY ON THE PREVALENCE OF DIABETES IN TUBERCULOSIS PATIENTS IN NIDCH HOSPITAL, DHAKA

A dissertation Submitted to the Department of Pharmacy for the Partial Fulfillment of the Degree of Bachelor of Pharmacy.

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DECLARATION BY THE RESEARCH CANDIDATE

I, Tanzila Tofaz, ID: 2012-1-70-004, hereby declare that the dissertation entitled **"A Survey on the Prevalence of Diabetes in Tuberculosis patients in NIDCH Hospital, Dhaka "** submitted to the Department of Pharmacy, East West University, in the partial fulfillment of the requirement for the degree of Bachelor of Pharmacy (Honors) is a genuine & authentic research work carried out by me. The contents of this dissertation, in full or in parts, have not been submitted to any other institute or University for the award of any degree or Diploma of Fellowship.

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CERTIFICATION BY THE SUPERVISOR

This is to certify that the dissertation, entitled **"A Survey on the Prevalence of Diabetes in Tuberculosis patients in NIDCH Hospital, Dhaka"** is a bona fide research work done by Tanzila Tofaz (ID: 2012-1-70-004), in partial fulfillment of the requirement for the degree of Bachelor of Pharmacy under my supervision.

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ENDORSEMENT BY THE CHAIRPERSON

This is to certify that the dissertation, entitled **"A Survey on the Prevalence of Diabetes in Tuberculosis patients in NIDCH Hospital, Dhaka"** is a bona fide research work done by Tanzila Tofaz (ID: 2011-1-70-004), under the guidance of **Tilka Fannana**, Senior Lecturer, in partial fulfillment of the requirement for the degree of Bachelor of Pharmacy.

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ACKNOWLEDGEMENTS

Above all, I express my gratitude to Almighty Allah for all the bounties granted to me & only with HIS guidance & help this achievement has become possible.

It is my pleasure & proud privilege to express my heartiest regards & gratitude to my respected teacher & supervisor **Mrs. Tilka Fannana**, Senior Lecturer, Department of Pharmacy, East West University, for her expert supervision, constructive criticism, valuable advice, optimistic counseling, constant support & continuous backup & encouragement throughout every phase of the project as well as to prepare this dissertation.

I would also like to put forward my most sincere regards & profound gratitude to **Dr. Shamsun Nahar Khan**, Associate Professor & Chairperson, Department of Pharmacy, East West University, for giving me the opportunity to conduct such an interesting project & for facilitating a smooth conduction of my study.

I would also like to thank my fellow research group partner for her immense support & contribution in my research work. I would also like to thank each & every member of my batch **2012-1,** who helped me instantaneously when I needed the most while working on this research paper.

And at the end, I would like to thank my family for their endless inspiration, support & care during my research work.

DEDICATION

This research paper is dedicated to my beloved parents for their unconditional support.

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List of Abbreviations

TB	Tuberculosis
MDR-TB	Multi-Drug Resistant Tuberculosis
XDR-TB	Extensively Drug Resistant Tuberculosis
DOTS	Directly Observed Treatment Strategy
WHO	World Health Organization
HIV	Human Immunodeficiency Virus
TST	Tuberculin Skin Test
MTb	*Mycobacterium tuberculosis*
RIF	Rifampicin
PMDT	Programmatic Management of Drug-resistant TB
NTP	National Tuberculosis Control Program
CNS	Central Nervous System
GI	Gastro-Intestine
DR-TB	Drug Resistant Tuberculosis
MDGs	Millennium Development Goals
NIDCH	National Institute of Diseases of Chest and Hospital
NIDDM	Non-Insulin-Dependent Diabetes Mellitus

DKA	Diabetic Ketoacidosis
IV	Intravenously
HbA1c	Glycosolated Hemoglobin A1c
TUs	Tuberculosis Units
RNTCP	Revised National Tuberculosis Control Programme

Abstract

Since the early part of the 20th century, clinicians have observed an association between diabetes mellitus (DM) and TB, although they were often unable to determine whether DM caused TB or whether TB led to the clinical manifestations of DM. Several studies have suggested that diabetes mellitus (DM) increases the risk of active tuberculosis (TB). The rising prevalence of DM in TB-endemic areas may adversely affect TB control. Experts have raised concerns about the merging epidemics of DM and TB, especially in low- to middle-income countries, such as India and China, that are experiencing the fastest increase in DM prevalence and the highest burden of TB in the world. As Bangladesh is also a middle income & developing country, so it is very important to figure out the picture of association of DM & TB in Bangladesh. The objective of our study was to conduct a survey among 100 TB and MDR-TB patients of NIDCH and study the prevalence of DM in such patients with associated risk factors.

In our study 53% were males and 47% were females. Among them 61% were MDR-TB patient & 39% were TB patients.37% were diabetic & 63% were Non-diabetic. We found diabetic TB patients are usually middle aged male than those without DM. This may be due to an association of type 2 DM with older age. We found that males (62.17%) are more prone to TB & DM than females (38. 83%). We observed that mostly suffered symptoms of diabetic TB were increased thirst (32%), frequent urination (27%) & fatigue (26%) and weakness (59%). Majority of the patients (80%) had no knowledge that diabetes can increase the chance of TB incidence. So unawareness is a major issue which needs to be addressed by health care professionals. In our study, majority of TB patients having DM (24.32%) were illiterate or from college whereas minority of TB patients having DM (13.52%) were from primary education. We also observed that the clinical characteristics of TB do not differ much amongst diabetic and non-diabetic patients. From our study we also found that each & every type of TB whether it is pulmonary or extra-pulmonary, has no variation with Diabetes.

Key Words: *Tuberculosis, Diabetes Mellitus, Mycobacterium tuberculosis, DR-TB, NIDCH.*

CHAPTER ONE
INTRODUCTION

Introduction

1.1 Overview

The link between diabetes mellitus and tuberculosis has been recognized for centuries. In recent decades, tuberculosis incidence has declined in high-income countries, consequently incidence remains high in countries that have poor tuberculosis control strategies, high rates of infection with HIV, high prevalence of malnutrition and crowded living conditions, At the same time, incidence of diabetes mellitus has been a worldwide issue fueled with obesity.

Surprisingly there is growing evidence that diabetes mellitus is an important risk factor for tuberculosis and might affect disease presentation and treatment response. This may also make the tuberculosis patient multi drug resistant. Furthermore, tuberculosis might induce glucose intolerance and worsen glycaemic control in people with diabetes. Various studies have been done in various countries on this burning issue and it has been shown that DM increases the risk of tuberculosis along this MDR-Tb. It has been also proved that DM increases the risk of active tuberculosis (TB) by approximately three times. A bidirectional association between them has been demonstrated by many researchers (Stevenson *et al.*, 2003).

The link of DM and TB is more prominent in developing countries where TB is endemic and the burden of diabetes mellitus is increasing. The association between diabetes and tuberculosis may be the next challenge for global tuberculosis control worldwide. Proper planning and collaboration are necessary to reduce the dual burden of diabetes and TB. One model similar to the TB-HIV program for prevention, screening and treatment of both diseases can be the best approach. Few studies in lower income countries have explored this relationship in light of growing DM prevalence in the developing world. In this paper, we studied the prevalence of diabetes in tuberculosis patients in NIDCH hospital, with some associated risk factors.

1.2 Tuberculosis

Tuberculosis (TB) is contagious and airborne disease. It is an infectious bacterial disease caused by *Mycobacterium tuberculosis*, which most commonly affects the lungs. Nearly one-third of the global population, i.e. over two billion people, is infected with *Mycobacterium tuberculosis* and thus at risk of developing the disease. It causes ill-health among millions of people each year and ranks as the second leading cause of death from an infectious disease worldwide, after the Human Immunodeficiency Virus (HIV). TB is transmitted from person to person via droplets from the throat and lungs of people with the active respiratory disease. A person needs to inhale only a few of these germs to become infected. It can also affect the viscera like lymph nodes, bones, joints, skin, the central nervous system, the urinary tract and the abdomen, or it can give a disseminated form of disease (Miliary tuberculosis).

About one-third of the world's population has latent TB, which means people have been infected by TB bacteria but are not (yet) ill with disease and cannot transmit the disease. People infected with TB bacteria have a lifetime risk of falling ill with TB of 10%. However, people with compromised immune systems, such as people living with HIV, malnutrition or diabetes, or people who use tobacco, have a much higher risk of falling ill (WHO, 2015).

1.3: Pathophysiology of Tuberculosis

Once inhaled, the infectious droplets settle throughout the airways. The majority of the bacilli are trapped in the upper parts of the airways where the mucus-secreting goblet cells exist. The mucus produced catches foreign substances, and the cilia on the surface of the cells constantly beat the mucus and its entrapped particles upward for removal. This system provides the body with an initial physical defense that prevents infection in most persons exposed to tuberculosis.

Bacteria in droplets that bypass the mucociliary system and reach the alveoli are quickly surrounded and engulfed by alveolar macrophages, the most abundant immune effector

cells present in alveolar spaces. These macrophages, the next line of host defense, are part of the innate immune system and provide an opportunity for the body to destroy the invading mycobacteria and prevent infection. Macrophages are readily available phagocytic cells that combat many pathogens without requiring previous exposure to the pathogens. Several mechanisms and macrophage receptors are involved in uptake of the mycobacteria. The mycobacterial lipoarabinomannan is a key ligand for a macrophage receptor. The complement system also plays a role in the phagocytosis of the bacteria. The complement protein C3 binds to the cell wall and enhances recognition of the mycobacteria by macrophages. Opsonization by C3 is rapid, even in the air spaces of a host with no previous exposure to *M. tuberculosis*. The subsequent phagocytosis by macrophages initiates a cascade of events that results in either successful control of the infection, followed by latent tuberculosis, or progression to active disease, called primary progressive tuberculosis. The outcome is essentially determined by the quality of the host defenses and the balance that occurs between host defenses and the invading mycobacteria.

After being ingested by macrophages, the mycobacteria continue to multiply slowly, with bacterial cell division occurring every 25 to 32 hours. Regardless of whether the infection becomes controlled or progresses, initial development involves production of proteolytic enzymes and cytokines by macrophages in an attempt to degrade the bacteria. Released cytokines attract T lymphocytes to the site, the cells that constitute cell-mediated immunity. Macrophages then present mycobacterial antigens on their surface to the T cells. This initial immune process continues for 2 to 12 weeks; the microorganisms continue to grow until they reach sufficient numbers to fully elicit the cell-mediated immune response, which can be detected by a skin test.

For persons with intact cell-mediated immunity, the next defensive step is formation of granulomas around the *M. tuberculosis* organisms (Figure 1.1).

These nodular-type lesions form from an accumulation of activated T lymphocytes and macrophages, which creates a micro-environment that limits replication and the spread of the mycobacteria. This environment destroys macrophages and produces early solid necrosis at the center of the lesion; however, the bacilli are able to adapt to survive. In fact,

M. tuberculosis organisms can change their phenotypic expression, such as protein regulation, to enhance survival. By 2 or 3 weeks, the necrotic environment resembles soft cheese, often referred to caseous necrosis, and is characterized by low oxygen levels, low pH, and limited nutrients. This condition restricts further growth and establishes latency. Lesions in persons with an adequate immune system generally undergo fibrosis and calcification, successfully controlling the infection so that the bacilli are contained in the dormant, healed lesions. Lesions in persons with less effective immune systems progress to primary progressive tuberculosis.

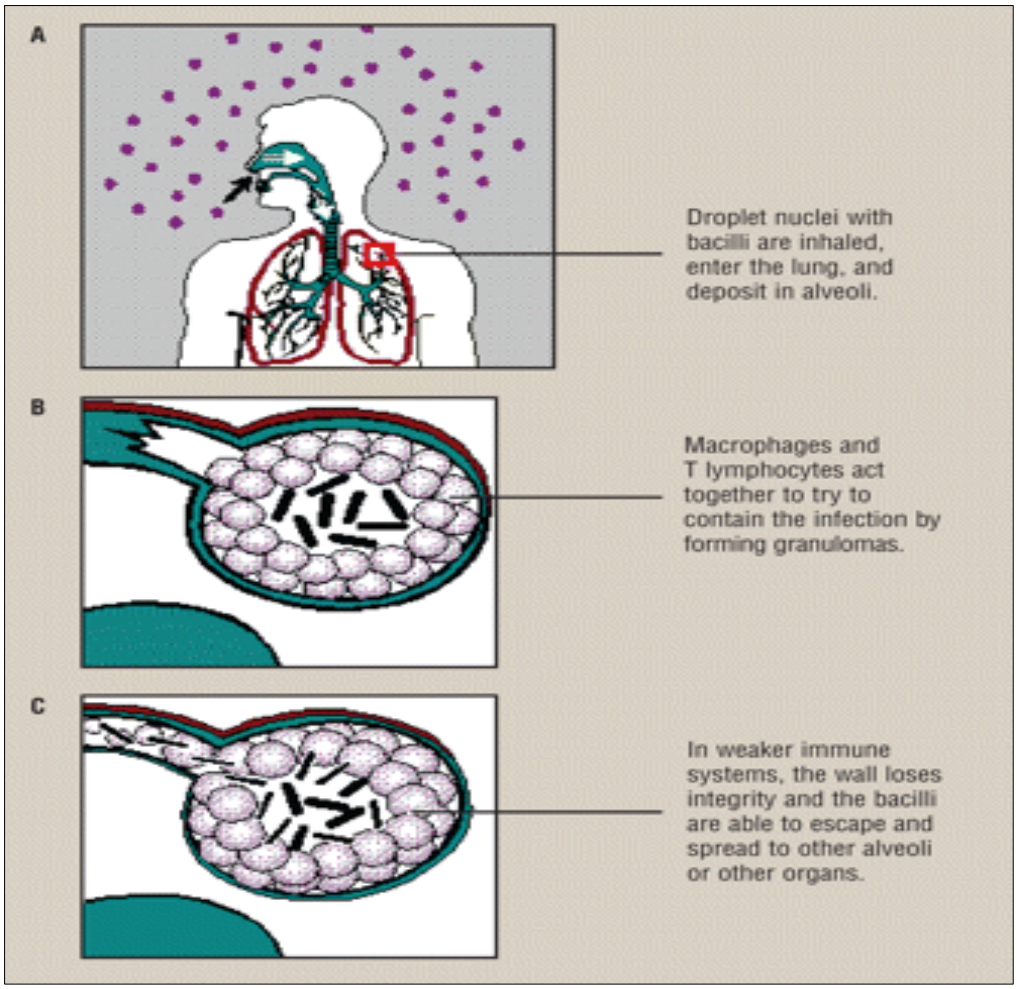

Figure 1.3.1: Pathophysiology of tuberculosis: inhalation of bacilli (A), containment in a granuloma (B), and breakdown of the granuloma in less immunocompetent individuals (C) (Knechel,2009).

1.4: Types of TB:

TB is divided into 2 categories: Pulmonary and Extra Pulmonary.

1.4.1Pulmonary TB

This type of TB includes-

- **Primary Tuberculosis Pneumonia**

It is an uncommon type of TB presents as pneumonia. This results with a complication of tuberculosis in which caseous material is inhaled into the bronchi, leading to bronchopneumonia or lobarpneumonia.

- **Tuberculous Pleuritis**

It develops soon after initial infection. Tuberculous pleuritis is an infectious disease (Pleural infection by *Mycobacterium tuberculosis)*, which is characterized by protein-rich effusions and abundant *M. tuberculosis*.

This is an inflammation of the membrane that surrounds and protects the lungs (the pleura). Inflammation occurs when an infection or irritates the pleural surface by protein-rich effusions and abundant *M. tuberculosis*.

- **Cavitary TB**

Cavitary TB involves the upper lobes of the lung. The bacteria cause progressive lung destruction by forming cavities, or enlarged air spaces. This type of TB occurs in reactivation disease. The upper lobes of the lung are affected because they are highly oxygenated (an environment in which *M. tuberculosis* thrives). Cavitary TB can, rarely, occur soon after primary infection.

- **Miliary TB**

Miliary TB is disseminated TB. "Miliary" describes the appearance on chest x-ray of very small nodules throughout the lungs that look like millet seeds. Miliary TB can occur shortly after primary infection.

- **Laryngeal TB**

TB infects the larynx, or the vocal chord area. It is extremely infectious.

1.4.2 Extra Pulmonary TB

This kind of TB includes:

- **Lymph Node Disease**

Lymph nodes contain macrophages that capture the bacteria. Any lymph node can harbor uncontrolled replication of bacteria, causing the lymph node to become enlarged. The infection can develop a fistula (passageway) from the lymph node to the skin.

- **Tuberculosis Peritonitis**

M. tuberculosis can involve the outer linings of the intestines and the linings inside the abdominal wall, producing increased fluid, as in tuberculosis pleuritis. Increased fluid leads to abdominal distention and pain. Patients are moderately ill and have fever.

- **Tuberculosis Pericarditis**

The membrane surrounding the heart (the pericardium) is affected in this condition. This causes the space between the pericardium and the heart to fill with fluid, impeding the heart's ability to fill with blood and beat efficiently.

- **Osteal Tuberculosis**

Infection of any bone can occur, but one of the most common sites is the spine. Spinal infection can lead to compression fractures and deformity of the back.

- **Renal Tuberculosis**

This can cause asymptomatic pyuria (white blood cells in the urine) and can spread to the reproductive organs and affect reproduction. In men, epididymitis (inflammation of the epididymis) may occur.

- **Adrenal Tuberculosis**

TB of the adrenal glands can lead to adrenal insufficiency. Adrenal insufficiency is the inability to increase steroid production in times of stress, causing weakness and collapse.

- **TB Meningitis**

M. tuberculosis can infect the meninges (the main membrane surrounding the brain and spinal cord). This can be devastating, leading to permanent impairment and death. TB can be difficult to discern from a brain tumor because it may present as a focal mass in the brain with focal neurological signs (WHO, 2014).

1.5: Signs and Symptoms of TB

Individuals infected with TB can have latent TB infection or active TB disease. Those with latent TB infection do not exhibit symptoms and cannot spread the infection to others, whereas those with active TB disease exhibit a range of symptoms and are contagious. In healthy people, infection with *Mycobacterium tuberculosis* often causes no symptoms, since the person's immune system acts to "wall off" the bacteria (Khanum, Sultana and Dhar, 2013).

Pulmonary TB should be presumed in a person who presents with persistent cough for three weeks or more, with or without production of sputum and despite the administration of a non-specific antibiotic. Thus Presumptive TB refers to a patient who presents with symptoms or signs suggestive of TB (previously known as a TB suspect).

Often a patient with pulmonary TB has one or more of the following symptoms in addition to cough:

- Respiratory symptoms: shortness of breath, chest pain, coughing up of blood
- General symptoms: loss of weight, loss of appetite, fever, night sweats

Sputum microscopy for AFB should always be requested for a patient, who has cough for three weeks or longer, even in the absence of any other symptoms.

Signs and symptoms of extra-pulmonary TB depend on the site involved. Most common examples are:

- TB lymphadenitis: swelling of lymph nodes
- Pleural effusion: fever, chest pain, shortness of breath
- TB arthritis: pain and swelling of joints
- TB of the spine: radiological findings with or without loss of function
- Meningitis: headache, fever, stiffness of neck and subsequent mental confusion (NTP, 2013).

1.6 Diagnosis & Treatment of TB

The current routine diagnostic tests for TB are chest x-ray, tissue culture, tuberculin skin test (TST) and acid-fast staining - all have their limitations. A chest x-ray alone is inconclusive; a tissue culture takes too long to produce a result; the TST (Tuberculin skin test) lacks specificity and reliability; and acid-fast staining depends on a large number of bacteria in the sputum to give an accurate reading (Khanum, Sultana and Dhar, 2013)

Besides all these things diagnosis & treatment process is followed by:

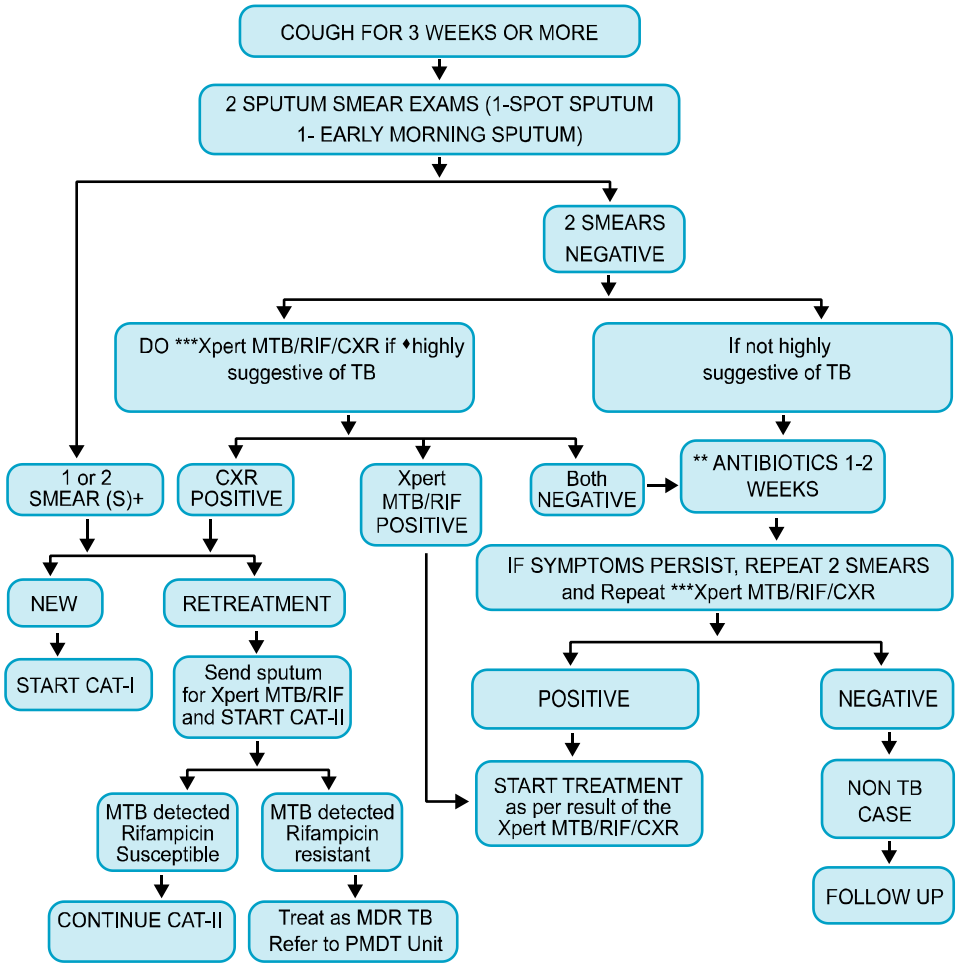

Figure 1.6.1: Flow Chart Followed for Diagnosis & Treatment of TB

Here,

*Previous history of treatment 1 month: CAT II.

**Exclude Clarithromycin, Quinolones, Amoxyclavulanate.

***Xpert MTB/RIF should be advised by qualified physician. Do Xpert MTB/RIF first` if both Xpert MTB/RIF and CXR is available.

(S) Highly suggestive of TB: Presumptive TB cases with cough for 3 weeks, fever and weight loss (NTP, 2013).

Table 1.6.1: Standardized Treatment Regimen for Each Diagnostic Category (Adults)

TB Diagnostic Category	Type of Patient	Treatment Regimen	
		Intensive Phase (Daily)	**Continuation Phase (Daily)**
Cat.I	- New smear-positive - bacteriologically positive PTB patients - New smear-negative -PTB - New Extra-pulmonary TB - New concomitant/ associated HIV/AIDS	2(HRZE) Here, H=Isoniazid R=Rifampicin Z=Pyrazinamide E=Ethambutol	4 (HR) Here, H=isoniazid R=Rifampicin
Cat. II	- Sputum smear-positive PTB with history of treatment of one month or more - Relapse - Treatment failure after Cat. I Treatment after loss to follow up - Others	1(HRZE) 2(HRZE)/S Here, H=Isoniazid R=Rifampicin Z=Pyrazinamide E=Ethambutol S=Streptomycin	5 (HRE) Here, H=Isoniazid R=Rifampicin E=Ethambutol

Dosages of FDC Tablets:

FDC tablets are composed as follows:

4FDC: Isoniazid 75 mg + Rifampicin 150 mg + Pyrazinamide 400 mg + Ethambutol 275 mg

2FDC: Isoniazid 75 mg + Rifampicin 150 mg

3FDC: Isoniazid 75 mg + Rifampicin 150 mg + Ethambutol 275 mg

* The dose of streptomycin should not exceed 500 mg daily after the age of 50 years (NTP, 2013).

1.7 Side Effects of TB Treatment

Patients taking Pulmonary TB or Extra pulmonary TB regimen very frequently suffer from the side effects. Anti-tuberculosis drugs show some very common side effects including nausea, vomiting, diarrhea, hepatotoxicity, dermatological problems such as flushing etc. It is also evident that due to the termination of therapy in up to 23% of patients during the intensive phase, occurrence of hepatitis, dyspepsia, exanthema and arthralgia is also very common. The most challenging part for a TB patient is to protect him from being drug resistant.

1.7.1 Side Effects Associated with Isoniazid

- **GI Intolerance:**
- Nausea, abdominal pain common
- Vomiting less common
- **Peripheral Neuropathy:**
- Burning, tingling
- Numbness of fingers/toes (usually toes first)
- **Rash:**
- Mild rash or itching
- Erythematous rash with fever and/or mucousmembrane involvement
- **Tyramine Poisoning**:

- may cause flushing, palpitations when taken with foods high in tyramine (red wine, aged cheese)

- **CNS Toxicity**:
- Confusion
- Psychosis
- Insomnia
- Headache

- **Fatigue**
- **Lupus-Like Syndrome**:
- Fever
- Joint pain
- Fatigue
- Weight loss

1.7.2 Side Effects Associated with Rifampicin

- **GI Side Effects**
- **Orange Urine/Body Fluids (Sweat)**
- **Flu-Like Syndrome:**
- Fevers
- Myalgia
- Arthralgia
- Headache

- **Interstitial Nephritis (Rare):**
- Kidney failure due to hypersensitivity reaction to rifampin
- May be accompanied by rash, fever, eosinophilia in blood

1.7.3 Side effects associated with Pyrazinamide

- **GI Symptoms**
- **Arthralgia (Joint Pain)**
- **Rash**

- **Hyperuricemia (Elevateduric Acid)**

1.7.4 Side Effects Associated with Ethambutol

- **Optic Neuritis**:
  - Blurred Vision
  - Red/Green Color Blindness

1.7.5 Side Effects Associated with Moxifloxacin:

- **Nausea/GI side effects**
- **CNS:**

- Headache
- Insomnia
- Confusion

- **Tendonitis**
- **Tendon Rupture** (Gadkowski, 2012).

1.8 Multi Drug Resistant TB

The bacterium that causes tuberculosis (TB) can develop resistance to the antimicrobial drugs used to cure the disease. Multidrug-resistant tuberculosis (MDR-TB) is TB that does not respond to at least isoniazid and rifampicin, the two most powerful anti-TB drugs (WHO, 2015).

Resistance to one or several forms of treatment occurs when the bacteria develops the ability to withstand antibiotic attack and relays that ability to its offspring. Since that entire strain of bacteria inherits this capacity to resist the effects of the various treatments, resistance can spread from one person to another.

Although the causes for multi drug resistance could be microbial, clinical and/or programmatic, Drug Resistant TB is essentially a manmade phenomenon. From a

microbiological perspective, resistance is caused by a genetic mutation that makes a drug ineffective against the mutant bacilli. From a clinical and programmatic perspective, it is an inadequate or poorly administered treatment regimen that allows a Drug Resistant strain to become the dominant strain in a patient infected with TB. It is important to note, the ongoing transmission of infection from MDR-TB cases in a population contributes to new primary Drug Resistant cases. In fact, MDR-TB is very difficult to be treated and may lead one to death very often (PMDT, 2013).

1.9 Treatment of MDR-TB

Treatment of multi drug resistant TB (MDR-TB) is more difficult than the treatment of drug susceptible TB, and it requires the use of "second line" or reserve drugs that are costlier, cause more side effects, and the drugs must be taken for up to two years. Cure rates for MDR-TB are lower, typically ranging from around 50% to 70%.

The current WHO guidelines on treatment regimens for MDR-TB recommend an intensive phase of treatment of 8 months and a total duration of treatment of 20 months for most patients. According to WHO, patients who may have a high risk of relapse and acquired resistance, follow-up after treatment completion is aimed and patients should be under close monitoring for a period of at least 12 months beyond the end of treatment. Proper attention to drug regulatory and ethical issues is needed to facilitate and enhance current WHO guidelines on the treatment of MDR-TB (WHO, 2015).

The drugs that are used for the treatment of drug resistant TB are grouped according to how effective they are, how much experience there is of their use and the drug class. All the "first line" anti TB drugs are in Group 1, apart from streptomcycin which is classified with the other injectable agents in Group 2.

Table 1.9.1: Classification of Drugs Used for Drug Resistant TB

Grouping	Drugs	Remarks
Group 1: First-Line Oral Agents	Isoniazid (H); Rifampicin (R); Ethambutol (E); Pyrazinamide (Z);	- These are the most potent and best tolerated drugs. - Pyrazinamide is used in the Standard MDR-TB regimens because it is thought to retain some susceptibility in many cases of MDR-TB. - However, caution is warranted, because whenever a drug was used in a previous regimen that failed, it should not be heavily relied upon as a key drug.
Group 2: Injectable Agents	Kanamycin (Km); Amikacin (Am); Capreomycin (Cm); Streptomycin (S)	- All regimens to treat MDR-TB or XDR TB includes; an injectable agent. Given the greater ototoxicity with streptomycin and high rates of streptomycin resistance in DR TB cases, it will not be used to treat DR TB in Bangladesh. Amikacin and kanamycin are

		considered to be very similarand have a high frequency of cross-resistance. - There is low cross-resistance with kanamycin (oramikacin) and capreomycin.
Group 3: Fluoroquinolones	Moxifloxacin (Mfx); Levofloxacin (Lfx); Ofloxacin (Ofx)	- All patients should receive one of the fluoroquinolones. The most potent available fluoroquinolones in descending order based on invitro activity and animal studies are: moxifloxacin= gatifloxacin> levofloxacin>ofloxacin. - Levofloxacin is the fluoroquinolone on theStandard MDR-TB Regimen while moxifloxacin will be used in the Standard XDR TB Regimen.

Group 4: Oralbacteriostatic Second Line Agents	Ethionamide (Eto); Prothionamide (Pto); Cycloserine (Cs); *p*-aminosalicylic acid (PAS)	- The Standard MDR-TB Regimen in Bangladeshemploys at least two agents from Group 4. In general, avoid the combination of PAS with ethionamide (or prothionamide) because ofincreased gastrointestinal side effects and hypothyroidism, however, sometimes thiscombination is needed. The drugs in Group 4 may be started at a low dose and escalated over seven days (this is called drug ramping).
Group 5: Agents with unclear role in DR TB treatment (not recommended by WHO for routine use in DR TB patients)	Clofazimine (Cfz); Linezolid (Lzd); Amoxicillin/Clavulanate (Amx/Clv); Clarithromycin	- These drugs are not recommended by the WHO for routine use in DR TB treatment because theircontribution to the efficacy of multidrug regimen is unclear. However, they can be used in cases of XDR TB. Only clofazimine and amoxicillin/clavulanate

	(Clr); Thioacetazone (Thz); Imipenem/Cilastatin (Ipm/Cln); High-dose Isoniazid (High-dose H);	are used routinely in Bangladesh for the Standard XDR TB regimen. Other drugs may be added in consultation with an expert in the treatment of XDR TB. If strains resistant to lowconcentrations of INH, but are susceptible to higherconcentrations, then high-dose INH can be considered.

*High-dose H is defined as 16–20 mg/kg/da.

* The recommended Standard MDR-TB Regimen is as follows:
8{Km-Z-Lfx (Ofx)-Eto-Cs}/12{Lfx (Ofx)-Eto- Cs-Z} (PMDT, 2013).

1.10 Status of Tuberculosis in Developing Countries

TB is present in all regions of the world and the Global Tuberculosis Report 2014 includes data compiled from 202 countries and territories. With the use of increased and improved national data. According to WHO in 2013, an estimated 9.0 million people developed TB and 1.5 million died from the disease. TB is slowly declining each year and it is estimated that 37 million lives were saved between 2000 and 2013 through effective diagnosis and treatment. However, given that most deaths from TB are preventable, the death toll from the disease is still unacceptably high and efforts to combat it must be accelerated if 2015 global targets, set within the context of the Millennium Development Goals (MDGs), are yet to be met. (WHO, 2014)

1.10.1 India

In India, according to the TB India Report 2014 by WHO, 40% of the country's population carries the *Mycobacterium tuberculosis* (the TB bacteria) in the passive form. About3.3 million people are suffering from one or the other type of TB and annually 276,000 lives are lost due to tuberculosis. As many as 9.4 million cases of TB are detected worldwide every year. India accounts for more than one-fifth of the same at about 1.98 million. It appears that a major change has come about in detection and treatment of tuberculosis cases between 1990 and 2014. It is believed that the incidence of tuberculosis has reduced from 216 per 100,000 per year in 1990 to 176 per 100,000 per year in the year 2014 in India, the tuberculosis mortality per 100,000 population having been reduced from 38 in year 1990 to 22 in 2014. In absolute numbers, mortality due to TB has scaled down from 330,000 to 270,000 annually (WHO, 2015).

1.10.2 China

China has an estimated 1 million new cases of tuberculosis every year, more than any country except India. In recent years, the Government has made great progress in TB control and prevention, resulting in a significant decline in the burden of TB. According to the report of WHO report- the estimated overall prevalence rate per 100,000 population fell from 215 in 1990, to 108 in 2010. The rate of decline was 2.2% per year between 1990 and 2000, and 4.7% per year between 2000 and 2010.TB mortality has declined rapidly, at an average rate of 8.6% per year between 1990 and 2010 and TB incidence rate was estimated to have declined by 3.4% per year since 1990 (WHO ,2015).

1.10.3 South Africa

South Africa is one of the countries with the highest burden of TB, with the World Health Organization (WHO) statistics giving an estimated incidence of 450,000 cases of active TB in 2013. So about 1% of the population of about 50 million develop active TB disease each year. This is worldwide the third highest incidence of any country after India and China, and the incidence has increased by 400% over the past 15 years (WHO, 2015).

1.10.4 Vietnam, Thailand & Zimbabwe

Almost 18,000 people die every year from TB in Vietnam. With an estimated 199new TB case/100,000 population, Vietnam ranks 12th among the 22 countries bearing 80% of the global TB.

Thailand is classified by WHO as a high burden TB and high burden HIV country. TB incidence was 119 per 100,000 populations in 2012 (estimated 80,000 new cases), and 13% of TB patients in 2012 were co-infected with HIV.

Zimbabwe is classified by WHO as a high burden country with TB. TB incidence was 562 per 100,000 populations in 2012 (Estimated 77,000 new cases) and 70% of TB patients associated with HIV (WHO, 2015).

1.11 Current Status of Tuberculosis in Bangladesh

Tuberculosis is one of the major health problems in Bangladesh. The country ranks sixth among the 22 countries with highest burden of TB in the world.

- Among the 22 high burden TB countries Bangladesh rank sixth in the world.
- 880 TB cases and 176 TB death occur in the country every day.
- According to WHO, the annual estimated incidence rate of TB in 225 per 100,000 populations
- TB Mortality is 45 per 100,000 populations
- Till 2007 total TB cases were 559,000 with 34,675 new cases 64,335 people died from TB
- Around 1/3 of TB cases go undetected.
- The prevalence (all cases) is estimated to be 434 per 100,000 populations (WHO, 2014).

Along with the international funds, the government imports anti-tuberculosis drugs from the other countries and has made the total treatment program free for patients. The DOTS

providers make sure that each reported TB patients are under their treatment regimen approved by WHO. The patients get their medications from their nearby health complex.

1.12 Current Status of MDR-TB in the Developing Countries

In 2013, the World Health Organization (WHO) estimated that 3.5% of new cases and 20.5% of previously treated cases of TB were of MDR (Multi Drug Resistant) TB. There were an estimated 300,000 new cases of MDR-TB among those cases of pulmonary TB that were reported to them. MDR-TB is just one of the different types of drug resistant TB, and is TB that is resistant to the TB drugs isoniazid and rifampicin.

It was also estimated that there were 480,000 new cases of MDR-TB among the world's 12 million prevalent cases of active TB. The number of prevalent cases of MDR-TB is important as it directly influences the active transmission of strains of MDR-TB. There were also approximately 210,000 deaths from MDR-TB and more than half of these patients were in India, China and the Russian Federation. (Tb Facts, 2015).

In China it is estimated there are 63,000 new multidrug-resistant tuberculosis (MDR-TB) cases among the 1 million notified new cases of TB every year. China contributes approximately one third of the world's MDR-TB. In India, various studies have found MDR-TB levels of about 3% in new cases and around 12-17% in retreatment cases (WHO,2015).

1.13 Current Status of MDR-TB in Bangladesh

Bangladesh is in risks of the spread of multiple-drug resistant tuberculosis (MDR-TB) as TB infected urban slum dwellers frequently change residence and most of the TB patients have high chance of occurrence of resistance. Currently multi-drug-resistant tuberculosis rate is 3.6% in new cases and 19% in re-treatment cases. World Health Organization (WHO) estimated 19% MDR-TB rate among previously treated cases and 3.6% among new cases.

Recognizing this burden of MDR-TB, Bangladesh government adopted 5 year DOTS plus pilot project. A national guideline has also been developed to manage all registered patients under

DOTS-plus project through approved standardized regimen. To diagnose and follow-up of cases a National TB Reference Laboratory has been established and functionalized in National Institute of Diseases of Chest and Hospital (NIDCH) (NTCP, 2013).

1.14: Diabetes Mellitus

Diabetes mellitus is a chronic disease caused by inherited and/or acquired deficiency in production of insulin by the pancreas, or by the ineffectiveness of the insulin produced. Such a deficiency results in increased concentrations of glucose in the blood, which in turn damage many of the body's systems, in particular the blood vessels and nerves.

The chronic hyperglycemia of diabetes is associated with long-term damage, dysfunction, and failure of various organs, especially the eyes, kidneys, nerves, heart, and blood vessels.

A number of medical risks are associated with type 1 diabetes. Many of them stem from damage to the tiny blood vessels in the eyes (called diabetic retinopathy), nerves (diabetic neuropathy), and kidneys(diabetic nephropathy). Even more serious is the increased risk of heart disease and stroke (WHO, 2014).

1.15: Types of Diabetes Mellitus

Diabetes mellitus has 2 types: Type 1 and Type 2

1.15.1: Type 1 Diabetes

Type 1 diabetes, previously called insulin-dependent diabetes mellitus (IDDM) or juvenile-onset diabetes, is very rare in case. This may account for 5 percent to 10 percent of all diagnosed cases of diabetes. Risk factors are less well defined for Type 1 diabetes than for Type 2 diabetes, but autoimmune, genetic, and environmental factors are involved in the development of this type of diabetes. (CDC, 2015)

1.15.2: Type 2 Diabetes

Type 2 diabetes was previously called non-insulin-dependent diabetes mellitus (NIDDM) or adult-onset diabetes. Type 2 diabetes may account for about 90 percent to 95 percent of all diagnosed cases of diabetes. Incidence of type 2 diabetes has been very common now-a-days. Risk factors for Type 2 diabetes include older age, obesity, family history of diabetes, prior history of gestational diabetes, impaired glucose tolerance, physical inactivity, and race/ethnicity. As Diabetes Mellitus inactivates the body defense mechanism slowly, so risks of association of different diseases along with DM is also very high. African Americans, Hispanic/Latino Americans, American Indians, and some Asian Americans and Pacific Islanders are at particularly high risk for type 2 diabetes. (CDC, 2015)

Type 2 diabetes can still cause major health complications, particularly in the smallest blood vessels in the body that nourish the kidneys, nerves, and eyes. Type 2 diabetes also increases the risk of heart disease and stroke. Insulin resistance, or lack of sensitivity to insulin, happens primarily in fat, liver, and muscle cells. People who are obese, more than 20% over their ideal body weight for their height, are at particularly high risk of developing type 2 diabetes and its related medical problems as obese people have insulin resistance (WebMD, 2015).

1.16 Pathogenesis of Diabetes Mellitus

1.16.1 Pathogenesis of Type 1 Diabetes

Type 1 diabetes is primarily a disease of the young given its peak incidence at the age of 10 to 12 years for girls and 12 to 14 years for boys; however, the disease can occur at any age, but most patients are diagnosed before age 20. Type 1 diabetes refers to cell-mediated autoimmune destruction of pancreatic beta islet cells, which leads to absolute insulin deficiency and predisposes individuals to diabetic ketoacidosis (DKA). The etiology is most often autoimmune in origin, but idiopathic destruction of beta islet cells without evidence of autoimmunity is also classified under this group. Although the presentation and progression is variable, all patients with DM-1 require insulin for survival.

The autoimmune nature of DM-1 has been intensively investigated, and it has long been assumed that the pathogenesis of the disease can be explained by an interplay between genetics and environment. The pathogenesis can be summarized as follows: in a genetically predisposed individual, (currently not well-defined) environmental factors trigger an autoimmune process (activation of T lymphocytes reactive to islet cell antigens) that leads to destruction of islet cells and insulin deficiency (Figure 1.3).

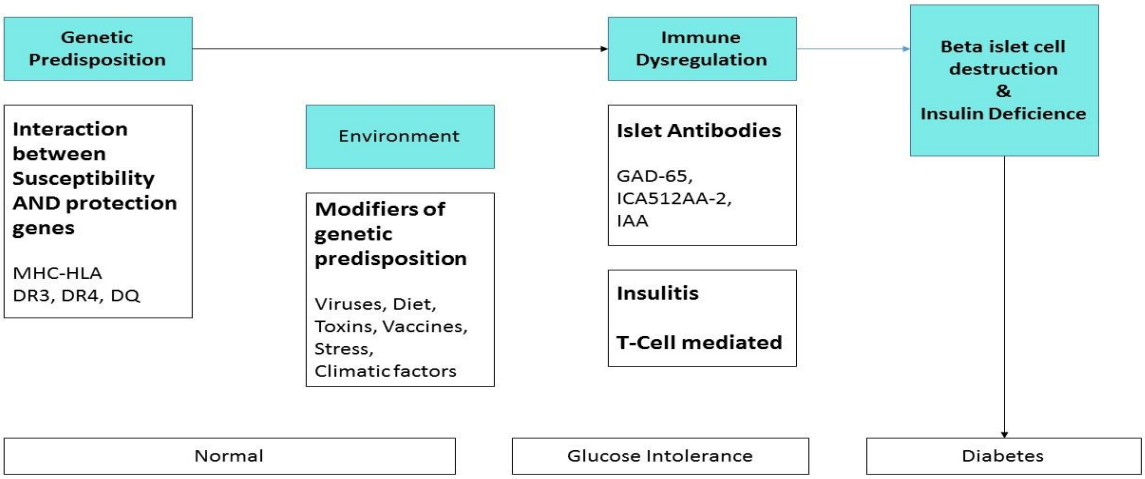

Figure 1.16.1: Pathogenesis of Type 1 Diabetes (Pittas, 2004)

1.16.2 Pathogenesis of Type 2 Diabetes

Type 2 diabetes (DM-2), previously known as NIDDM or adult-onset diabetes, is the most prevalent form of diabetes, accounting for over 90% of all cases of diabetes. Type 2 diabetes is characterized by varying degrees of insulin resistance and insulin deficiency. It is thought that the earliest defect in the pathogenesis of DM-2 is impaired insulin action or insulin resistance. Resistance to the action of insulin will result in impaired insulin mediated glucose uptake in the periphery (by muscle and fat), incomplete suppression of hepatic glucose output and impaired triglyceride uptake by fat. To overcome the insulin resistance (and therefore prevent abnormal fuel metabolism and maintain normal glucose and lipid levels), beta islet cells will increase the amount of insulin secreted. Higher circulating insulin levels will overcome the impedance to the action of insulin. This state of high insulin levels with euglycemia persists for many years. Abnormal fuel metabolism

(hyperglycemia and dyslipidemia) occurs when there is a mismatch between insulin requirements, as dictated by insulin resistance, and insulin supply, as dictated by beta cell function. Therefore, for DM-2 to develop, two defects are necessary: insulin resistance and insulin deficiency relative to the resistance (Figure 4).

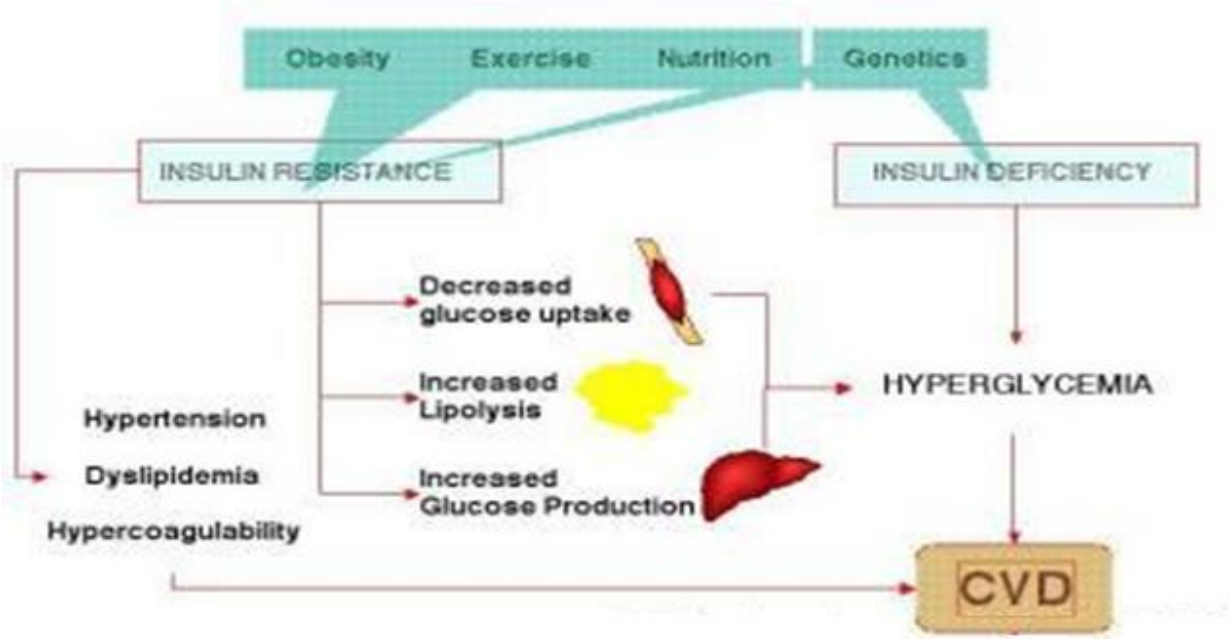

Figure 1.16.2: Pathogenesis of Type 2 DM (WHO,2014).

1.17 Symptoms of Diabetes Mellitus

Those who have both Type 1 & Type 2 diabetes may show the following symptoms-

a) Frequent urination
b) Excessive thirst,
c) Fatigue,
d) Sweating,
e) Unexplained weight loss,
f) Excessive hunger,
g) Sores that are slow to heal,
h) Feeling very tired much of the time
i) More infections than usual.

Besides these, nausea, vomiting, or stomach pains may accompany some of these symptoms in the abrupt onset of insulin-dependent diabetes, now called Type 1 diabetes (CDC, 2015).

1.18 Diagnosis of Diabetes (Type 1& 2)

Symptoms of type 1 diabetes often appear suddenly and are often the reason for checking blood sugar levels. Because symptoms of other types of diabetes and prediabetes come on more gradually or may not be evident some times.

Glycated hemoglobin (A1C) test is a blood test that indicates the average blood sugar level for the past two to three months. It measures the percentage of blood sugar attached to hemoglobin, the oxygen-carrying protein in red blood cells. Besides, blood sugar level can be frequently measured by a machine before and after taking meal.

If type 1 diabetes is suspected, then urine will be tested to look for the presence of a byproduct produced when muscle and fat tissue are used for energy when the body doesn't have enough insulin to use the available glucose (ketones). Doctor will also likely run a test to see if he has the destructive immune system cells associated with type 1 diabetes called autoantibodies (Mayoclinic, 2015).

1.19 Treatment of Type 1 & 2 Diabetes

1.19.1 Treatment of Type 1 Diabetes

Treatment for type 1 diabetes involves taking insulin, which needs to be injected through the skin into the fatty tissue below. Patients with type 1 diabetes mellitus (DM) require lifelong insulin therapy. Most require 2 or more injections of insulin daily, with doses adjusted on the basis of self-monitoring of blood glucose levels. Long-term management requires a multi-disciplinary approach that includes physicians, nurses, dietitians, and selected specialists.

Insulin injected subcutaneously is the first-line treatment of type 1 diabetes mellitus (DM). The different types of insulin vary with respect to onset and duration of action. Short-, intermediate-, and long-acting insulisns are available. Short-acting and rapid-acting insulins are the only types that can be administered intravenously (IV). Human insulin currently is the only species of insulin available in the United States; it is less antigenic than the previously used animal-derived varieties.

The methods of injecting insulin include:

- Syringes
- Insulin pens that use pre-filled cartridges and a fine needle
- Jet injectors that use high pressure air to send a spray of insulin through the skin
- Insulin pumps that dispense insulin through flexible tubing to a catheter under the skin of the abdomen.(WebMD, 2015)

1.19.2 Treatment of Type 2 Diabetes

There is no cure for diabetes. Type 2 diabetes can, however, be controlled with weight management, nutrition, and exercise. Unfortunately, Type 2 diabetes tends no progress, but yet diabetes medications are often needed to control the blood sugar level.

Pharmacologic therapy of type 2 diabetes has changed dramatically in the last 10 years, with new drugs and drug classes becoming available. These drugs allow for the use of combination oral therapy, often with improvement in glycemic control that was previously beyond the reach of medical therapy.

Agents used in diabetic therapy include the following:

- Biguanides
- Sulfonylureas
- Meglitinide derivatives
- Alpha-glucosidase inhibitors
- Thiazolidinediones (TZDs)
- Glucagonlike peptide–1 (GLP-1) agonists

- Dipeptidyl peptidase IV (DPP-4) Inhibitors
- Selective sodium-glucose transporter-2 (SGLT-2) inhibitors
- Insulins
- Amylinomimetics
- Bile acid sequestrants
- Dopamine agonists (WebMD, 2015).

1.20 Present Status of Diabetes Mellitus in the World

Diabetes mellitus is emerging as an epidemic all over the world, represents an important public health problem, and is of clinical concern. Type 1 diabetes has been estimated to affect approximately 19,000 people in the world's poorest countries but there is lack of good data on the disease prevalence in developing countries and in particular in Sub-Saharan Africa. Diabetes is a serious illness with multiple complications and premature mortality accounting for at least 10 % of total health care expenditure in many countries. The excess global mortality attributable to diabetes in the year 2000 was estimated to be 2.9 million deaths, equivalent to 5.2% of all deaths. Excess mortality attributable to diabetes accounted for 2-3 % of deaths in poorest countries (Yvonne, 2015).

1.21 Present Status of Diabetes Mellitus in Bangladesh

Diabetes mellitus, a chronic disease once thought to be uncommon in Bangladesh, but now it has emerged as an important public health problem. At present it is estimated that about 3.6 million people are affected throughout the country. The prevalence of diabetes in adult varied from 2.2 percent to 8.0 percent and the higher prevalence was found in urban areas predominantly among women. Unfortunately, there is still inadequate awareness about the real dimension of the problem in the general public. There is also lack of awareness about the existing interventions for preventing diabetes and management of complications. As diabetes increases the risk of other diseases, so it has been now a threat to the affected people along with the common people (Rahim, 2012).

1.22 Incidence of Diabetes Mellitus & Tuberculosis Together

Tuberculosis (TB) and diabetes mellitus (DM) are both important health issues. A bidirectional association between them has been demonstrated by many researchers. It has been an evident that Diabetes Mellitus (DM) increases the risk of active tuberculosis (TB) by approximately three times. Because of the impaired immune response, predisposed DM along with the active-TB affects the treatment regimen for tuberculosis patients. So increases in DM prevalence and persistently high TB incidence increases the importance of clarifying how DM affects TB disease presentation and response to anti-tuberculosis treatment (Magee *et al.*, 2015).

As the link of DM and TB is more prominent in developing countries where TB is endemic and the burden of diabetes mellitus is increasing, the association between diabetes and tuberculosis may be the next challenge for global tuberculosis control worldwide. (Baghaei *et al.*, 2013)

1.23 Global Relationship between TB & DM

The dual burden of tuberculosis (TB) and diabetes mellitus (DM) has increased over the past decade with DM prevalence increasing in countries already afflicted with a high burden of TB. The coexistence of the two conditions presents a serious threat to global public health.

The worldwide average prevalence of DM within the study period was 6.6±3.8% whereas TB incidence was 135.0±190.5 per 100,000. DM prevalence was highest in the Eastern Mediterranean (8.3±4.1) and West Pacific (8.2±5.6) regions and lowest in the Africa (3.5±2.6). TB incidence was highest in Africa (313.1±275.9 per 100,000) and South-East Asia (216.7±124.9) and lowest in the European (46.5±68.6) and American (47.2±52.9) regions. Only countries with high DM prevalence (>7.6%) showed a significant positive association with TB incidence (Badawi *et al.*, 2015).

1.24 Present Status of DM-TB Studies

In the early 20th century, the effect of DM on TB was large concern of investigators, but this was somewhat neglected in the second half of the 20th century with the emergence proper treatment for both diseases. In recent decades, with the increasing prevalence of TB, particularly Multi Drug Resistant TB (MDR-TB), and DM cases in the world, the relationship is re-emerging as a significant public health problem. The link of DM and TB is more prominent in developing countries where TB is endemic and the prevalence of DM is rising. At present along with the HIV-TB control studies, DM-TB studies defining their intermediate correlation is also a great challenge throughout the developing countries (Baghaei *et al.*, 2013).

CHAPTER TWO LITERATURE REIVIEW

Literature Review

2.1 Diabetes Mellitus Is Associated with Multidrug-Resistant Tuberculosis in Georgia

Diabetes Mellitus (DM) increases the risk of active tuberculosis (TB) by approximately three times. Global increases in DM prevalence and persistently high TB incidence increase the importance of clarifying the relationship between these two diseases.

Magee *et al.* performed a study with some aims such as-

1. To estimate the prevalence of DM and pre-DM using a glycosolated hemoglobin A1c (HbA1c) test among new adult patients with TB in Tbilisi, Georgia;
2. To estimate the association between DM and clinical characteristics at the time of diagnosis, including multi drug resistant TB (MDR-TB); and
3. To estimate the association between DM status and response to anti-tuberculosis treatment.

After this study, the prevalence of DM and pre-DM was 11.6% and 16.4%, respectively. The risk of poor anti-tuberculosis treatment outcomes was similar among patients with and those without DM (28.1%vs.23. 6%).This study showed that, DM and pre-DM were common among adults with newly diagnosed pulmonary TB and DM was associated with more clinical symptoms and MDR-TB (Magee et.al, 2014).

2.2 The Impact of Diabetes on Tuberculosis Treatment Outcomes: A Systematic Review

Baker *et al.* performed a systematic review and meta-analysis to quantitatively summarize evidence for the impact of diabetes on tuberculosis outcomes. His epidemiological studies have elucidated an association between diabetes mellitus (DM) and the development of TB disease. According to a recent systematic review, among cohort studies, people with DM had approximately three times the risk of developing TB disease. He studied that, the global burden of DM is rising; the prevalence is estimated to reach 438 million by 2030, and more

than 80% of the adult cases will be in newly developed or developing countries. The convergence of these two epidemics may lead to an increased incidence of TB disease, especially in low and middle income countries with increasing numbers of people with DM and prevalent TB disease.

The result of the study showed that Diabetes is associated with an increased risk of relapse but it did not find evidence for an increased risk of tuberculosis recurrence with drug resistant strains among people with diabetes (Baker *et al.*, 2011)

2.3 High Diabetes Prevalence among Tuberculosis Cases in Kerala, India

While diabetes mellitus (DM) is a known risk factor for tuberculosis, the prevalence among TB patients in India is unknown. Routine screening of TB patients for DM may be an opportunity for its early diagnosis and improved management and might improve TB treatment outcomes. Balakrishnan *et al.* conducted a cross-sectional survey of TB patients registered from June–July 2011 in the state of Kerala, India, to determine the prevalence of DM.

Balakrishnan *et al.* conducted this study to determine the overall prevalence of DM among TB patients and to assess whether routine screening of TB patients for DM within a program setting might yield previously undiagnosed DM cases, offering an opportunity for earlier detection and treatment of DM. The specific objectives of this study were to determine-

i) The overall prevalence of DM (self-reported and newly diagnosed) among TB patients registered for treatment in Kerala
ii) Additional yield of previously unknown DM as measured by glycosylated haemoglobin (HbA1c) and the Number needed to screen (NNS) to find a new case of DM and
iii) The factors associated with DM among TB patients.

Among 552 TB patients screened, 243(44%) had DM, 128(23%) had previously known DM and 115(21%) were newly diagnosed - with higher prevalence among males and those aged ≥ 50years. The result of the study has shown a high prevalence of DM in patients with

active TB, both for self-reported DM and for patients in whom the disease was not suspected, and supports routine screening of TB patients for DM (Balakrishnan *et al.*, 2012).

2.4 Diabetes, Pre-diabetes & Tuberculosis in an Asian Mega-City: Karachi, Pakistan

Codlin *et al.* sought to determine the first estimation of the contribution of DM to TB in the Asian mega-city of Karachi, Pakistan and studied that the risk of DM is between 2 and 6 times higher in South Asians compared to White Europeans and Pakistan has one of the highest burdens of TB worldwide.

They started their study in 2011, the Indus Hospital TB Program began routinely screening its patients for diabetes using HbA1c and TB-diabetes co-morbidity data for patients started on treatment between January 2011 and September 2012 was abstracted from electronic medical records.

Among 2258 TB patients screened, 30(7.8 %) had DM, 118 (28.4%) had previously known DM and 268 (64.4%) were newly diagnosed - with higher prevalence among males and those aged ≥ 50years. They also found the contribution of DM to the burden of TB in these populations. (Codlin *et al.*, 2012)

2.5 Diabetes Mellitus Increases the Risk of Active Tuberculosis

Jeon and Murray conducted a systematic review and a meta-analysis of observational studies assessing the association of DM and TB in order to summarize the existing evidence and to assess methodological quality of the studies. They undertook a systematic review to qualitatively and quantitatively summarize the existing evidence for the association between DM and TB, to examine the heterogeneity underlying the different studies, and to evaluate the methodological quality of the studies. As their aim was to summarize the effect of DM on TB, they did not include studies that investigated the reverse association.

After their study, the search yielded 13 observational studies (n=1,786; 212 participants) with 17,698 TB cases. Random effects meta-analysis of cohort studies showed that DM was associated with an increased risk of TB (relative risk=3.11). They found that DM was associated with an increased risk of TB regardless of study design and population. They also found that people with DM may be important targets for interventions such as active case finding and treatment of latent TB and efforts to diagnose, detect, and treat DM may have a beneficial impact on TB control (Jeon and Murray, 2008).

2.6 Bi-directional Screening for Tuberculosis and Diabetes: A Systematic Review

Jeon *et al.* wanted to assess the yield of finding additional TB or diabetes mellitus (DM) cases through systematic screening and to determine the effectiveness of preventive TB therapy in people with DM. Recognizing the opportunities offered by screening and preventive therapy, they systematically reviewed studies that had implemented screening or preventive therapy for TB among people with DM and those that screened for DM among patients with TB .This was done to assess the yield of finding additional TB or DM cases through active screening and to determine the effectiveness of preventive TB therapy in patients with diabetes.

Screening for TB in persons with DM, demonstrated that TB prevalence in this population is high, ranging from 1.7% to 36%, and increasing with rising TB prevalence in the underlying population as well as with DM severity. Result showed screening patients with TB for DM yielded high prevalence of DM (Jeon *et al.*, 2010).

2.7 Screening of Patients with Tuberculosis for Diabetes Mellitus in China

There is a high burden of both diabetes (DM) and tuberculosis (TB) in China, and this study aimed to assess feasibility and results of screening patients with TB for DM within the routine healthcare setting of six health facilities.

In China, Li *et al.* standardized a procedure for screening patients with TB for DM, a monitoring tool linked to the TB registration system and quarterly system of reporting were developed and agreed upon in the first half of 2011 with implementation starting in the second half of the year. This article describes the implementation, monitoring, results and challenges of screening patients with TB for DM within routine healthcare settings in the country.

This project showed that it is feasible to screen patients with TB for DM in the routine setting, resulting in a high yield of patients with known (226 patients) and newly diagnosed (227 patients) disease among 1090 patients. It also showed that free blood tests for glucose measurement and integration of TB and DM services may improve the diagnosis and management of dually affected patients (Li *et al.*, 2012).

2.8 Prevalence of Diabetes and Pre-Diabetes and Associated Risk Factors among Tuberculosis Patients in India

India has high TB burden along with rising DM prevalence. There are inadequate data on prevalence of DM and pre-diabetes among TB cases in India. Screening for DM in TB patients could improve DM case detection and early treatment and indirectly lead to better TB specific treatment outcomes

The aim of the study was to determine diabetes prevalence among a cohort of TB cases registered under Revised National Tuberculosis Control Program in selected TB units in Tamil Nadu, India, and assess pattern of diabetes management amongst known cases. This study was planned to determine the prevalence of diabetes and pre-diabetes amongst a cohort of TB patients registered in selected Tuberculosis Units (TUs) of Revised National Tuberculosis Control Program (RNTCP) in Tamil Nadu, India, and understand the pattern of diabetes management availed by the known diabetes.

Out of 827 TB patients, 209 (25.3%) had diabetes and prevalence of diabetes was significantly higher in men compared to women 27.5% vs 20.2% women. The result of the

study proved the association between DM and TB and showed the substantial evidence to support the fact that diabetes is an important risk factor for TB (Viswanathan *et al.*, 2012).

2.9 Smear Positive Pulmonary Tuberculosis Among Diabetic Patients at the Dessie Referral Hospital, Northeast Ethiopia

People with diabetes mellitus (DM) have a three times higher risk of developing active TB than people without diabetes. As there is not enough credible information on the burden of pulmonary tuberculosis (PTB) among DM patients in Ethiopia, in general, and in the city of Dessie, in particular, so Amare *et al.* performed this study with an aim to determine the prevalence and associated risk factors of smear positive PTB among diabetic patients at a referral hospital in Dessie.

The overall prevalence of smear positive Tuberculosis among TB suspected diabetic patients was high (6.2%) in Dessie. Pulmonary TB was occurring more often among patients with DM (>10 years), and among patients who had high blood glucose levels. Patients with a previous history of TB, history of contact with TB patients in the family, living in urban areas, and prolonged duration of DM were independent risk factors for the occurrence of active PTB (Amare *et al.*, 2013).

2.10 Diabetes Mellitus & Tuberculosis Facts & Controversies

Few studies in lower income countries have explored the relationship in light of growing DM prevalence in the developing world. Furthermore, the focus of most studies has been to assess the risk of TB in DM patients. In this paper, Baghaei *et al.* reviewed existing data and discussed the matters of controversy that will be helpful for determining priorities of research in different countries.

After the study, they reached in conclusion that improved understanding of the bidirectional relationship of the two diseases is necessary for proper planning and collaboration to reduce the dual burden of diabetes and TB. They also found that, in people with TB, it may be appropriate to actively screen for DM. Prevention, screening, and treatment of both diseases together is more effective (Baghaei *et al.*, 2013).

2.11 Diabetes Mellitus &Tuberculosis in Countries with High Tuberculosis Burdens: Individual Risks and Social Determinants

In order to appreciate the global population health significance of rising diabetes prevalence in the presence of persistent TB epidemics in settings where current TB burdens are high, Goldhaber- Fiebert *et al.* evaluated the relationship of diabetes and TB at both individual and country levels using population-representative data from largely lower income countries. They found that increase in TB prevalence (4.7%) and incidence over time were more likely to occur when diabetes prevalence (8.6%) also increased (Goldhaber- Fiebert *et al.*, 2013).

2.12 Diabetes Mellitus Increases the Risk of Active Tuberculosis: A Systematic Review of 13 Observational Studies

Several studies have suggested that diabetes mellitus (DM) increases the risk of active tuberculosis (TB). The rising prevalence of DM in TB-endemic areas may adversely affect TB control. Jeon & Murray conducted a systematic review and a meta-analysis of observational studies assessing the association of DM and TB in order to summarize the existing evidence and to assess methodological quality of the studies.

The studies showed that DM was associated with an increased risk of TB (relative risk = 3.11 in 17,698 patients). They noticed random effects of cohort studies which showed that DM was associated with an increased risk of TB. Their subgroup analyses showed that effect estimates were higher in non-North American studies (Jeon & Murray, 2008).

2.13 Association of Diabetes and Tuberculosis: Impact on Treatment & Post-Treatment Outcomes

The objective of this study was to determine the clinical consequences of pulmonary tuberculosis (TB) among patients with diabetes mellitus (DM). Jimenez-Corona *et al.* conducted a prospective study of patients with TB in Southern Mexico. From 1995 to 2010,

patients with acid-fast bacilli or *Mycobacterium tuberculosis* in sputum samples underwent epidemiological, clinical and microbiological evaluation.

They found that, the prevalence of DM, among 1262 patients with pulmonary TB was 29.63%. They also found that patients with DM and pulmonary TB had more severe clinical manifestations, delayed sputum conversion, a higher probability of treatment failure, recurrence and relapse (Jimenez-Corona *et al.*,2012).

CHAPTER THREE
METHODOLOGY

Methodology

3.1 Type of Study

The study was a clinical survey based study.

3.2 Aims & Objective of the Study

The objective of the present study was to conduct a survey among the TB and MDR-TB patients of NIDCH and study the prevalence of DM in such patients.

3.3 Study Area

The study was done in National Institute of Chest Disease and Hospital, Mohakhali, Dhaka-1212, Bangladesh.

3.4 Study Population

From July-September 2015, the survey was performed on 100 TB patients (MDR-TB **inclusive**), who were admitted into the hospital.

3.5 Inclusion Criteria

In this survey, all ages of patients were included having TB/MDR-TB (with or without DM).

3.6 Exclusion Criteria

In this survey, surgery patients and pregnant women were excluded.

3.7 Study Tool

To facilitate the study of prevalence of DM in TB patients in Dhaka, Bangladesh, a questionnaire was established in June 2015. Through this questionnaire, demographic information was collected

along with some risk factors that contribute to the prevalence of TB as well as prevalence of DM in TB and MDR-TB patients.

3.8 Questionnaire Development

The questionnaire was developed based on some common factors that lead to incidence of TB/MDR-TB along with prevalence of DM in such patients, in Dhaka, Bangladesh.

The questionnaire was prepared to obtain maximum clinical history of the patients along with demographic information and lifestyle factors that would help us link this information to our association of TB and MDR-TB with DM. The questionnaire was developed from the perspective of Bangladesh so that maximum accurate statistical data can be collected from the survey.

3.9 Data Analysis

After data collection, all the filled in questionnaires were checked and crosschecked in order to correct inconsistency in information and coding. Data were analyzed using Microsoft Office excel (Version 2007).

3.10 Ethics

This study was done without conflicting the ethical issues. Ethical consideration was checked by the research supervisor with the research policy of the East West University. Oral consent was taken prior to study from the participants. Written documents are also present of my weekly visit to NIDCH& conversation with patients.

CHAPTER FOUR
RESULT

Results

4.1 Patient Information

4.1.1 Demographic Information of Patients

Table 4.1.1: Demographic Information of Patients

Characteristic	Percentage
Gender	
Male	53
Female	47
Age	
≤ 20 years	18
21-30 years	22
31-40 years	31
41-50 years	17
51-60 years	11
≥60 years	1
Education level	
Illiterate	31
Primary	17
Secondary	15
College	24
Graduate	12
Post Graduate	1
Occupation	
Govt. Employee	8
Private Employee	9
Private Business	21
Housewife	27
Student	18
Garments worker	10
Farmer	7

Characteristic	Percentage
Income per Month (BDT)	
No income	33
≤ 5000	12
5000-10,000	36
10,000-25,000	16
≥25,000	3
Weight (kg)	
≤ 30	1
31-40	25
41-50	51
51-60	14
61-70	9

4.1.2 TB History

Table 4.1.2: TB History of the Patients

Diagnosed with TB for the First Time		Number of Times Diagnosed with TB	
Yes	43%	Once	52.63% (30)
No	57%	Twice	43.86% (25)
		Thrice	3.51% (2)

4.1.3 Family History of TB

Table 4.1.3: Family History of TB

Presence of Tb Patients in Family Currently		Family Members Previously Diagnosed with TB	
Yes	17%	Yes	25%
No	83%	No	75%

4.1.4 Living Condition

Table 4.1.4: Living Condition of the Patients

Number of People Living in The Household		Number of People Living in The Same Room	
1-2	11%	1	9%
3-4	32%	2	49%
5-6	33%	3	26%
7-8	16%	4	15%
9-10	4%	5	1%
11-12	4%		

4.1.5: Lifestyle Factors

Table 4.1.5: Life Style Factors of the Patients

Smoking Status		**Drinking Alcohol**		**Other Habituation (Betel Leaf)**	
Never smoked	66%	Never drunk	94%	Yes	18%
Past smoker	21%	Infrequent drinker	5%	No	82%
Current smoker	13%	Frequent drinker	1%		

4.2 Parameters of Tuberculosis

4.2.1 TB Symptoms

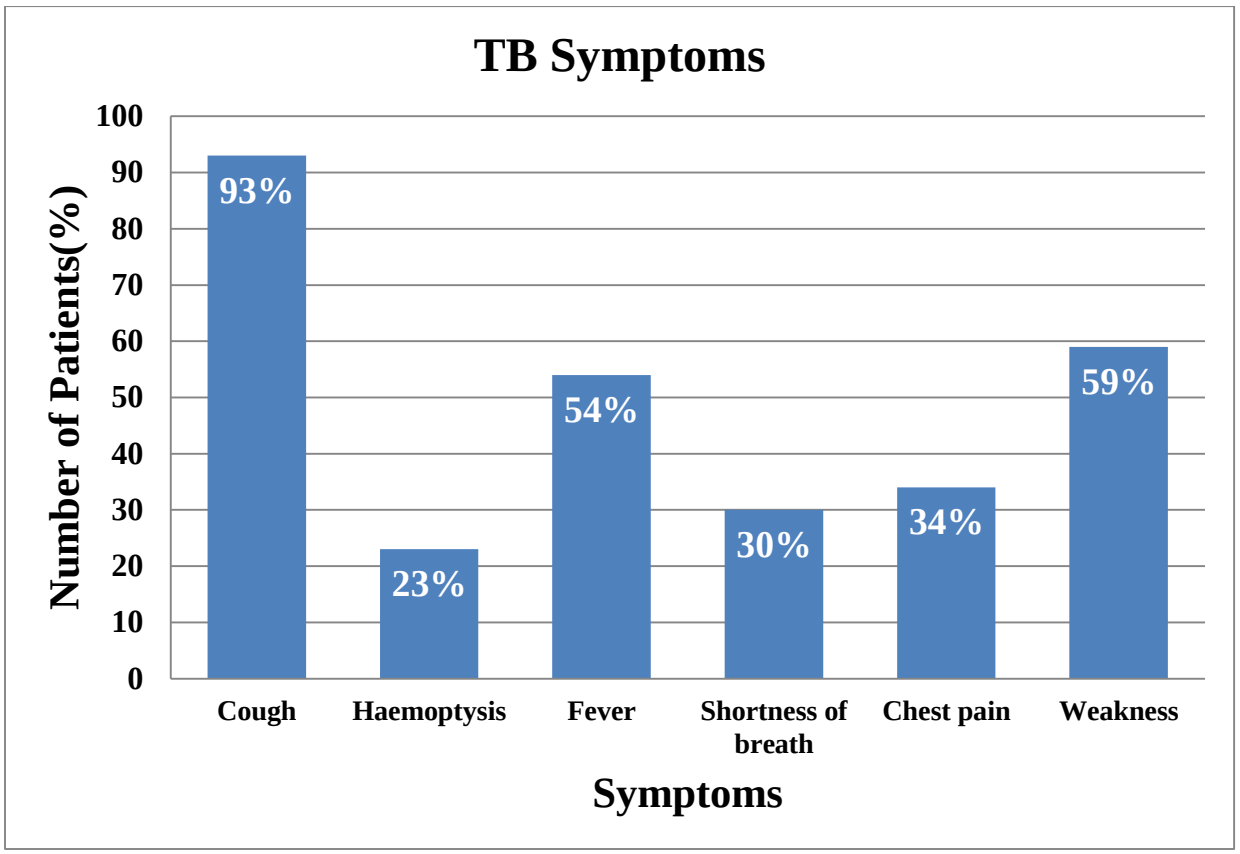

Figure 4.2.1: Symptoms of TB Patients

The study showed that majority of patients (93%) suffered from cough followed by weakness (59%) whereas minority of patients (23%) suffered from haemoptysis.

4.2.2 Time Elapsed Between Onset & Treatment

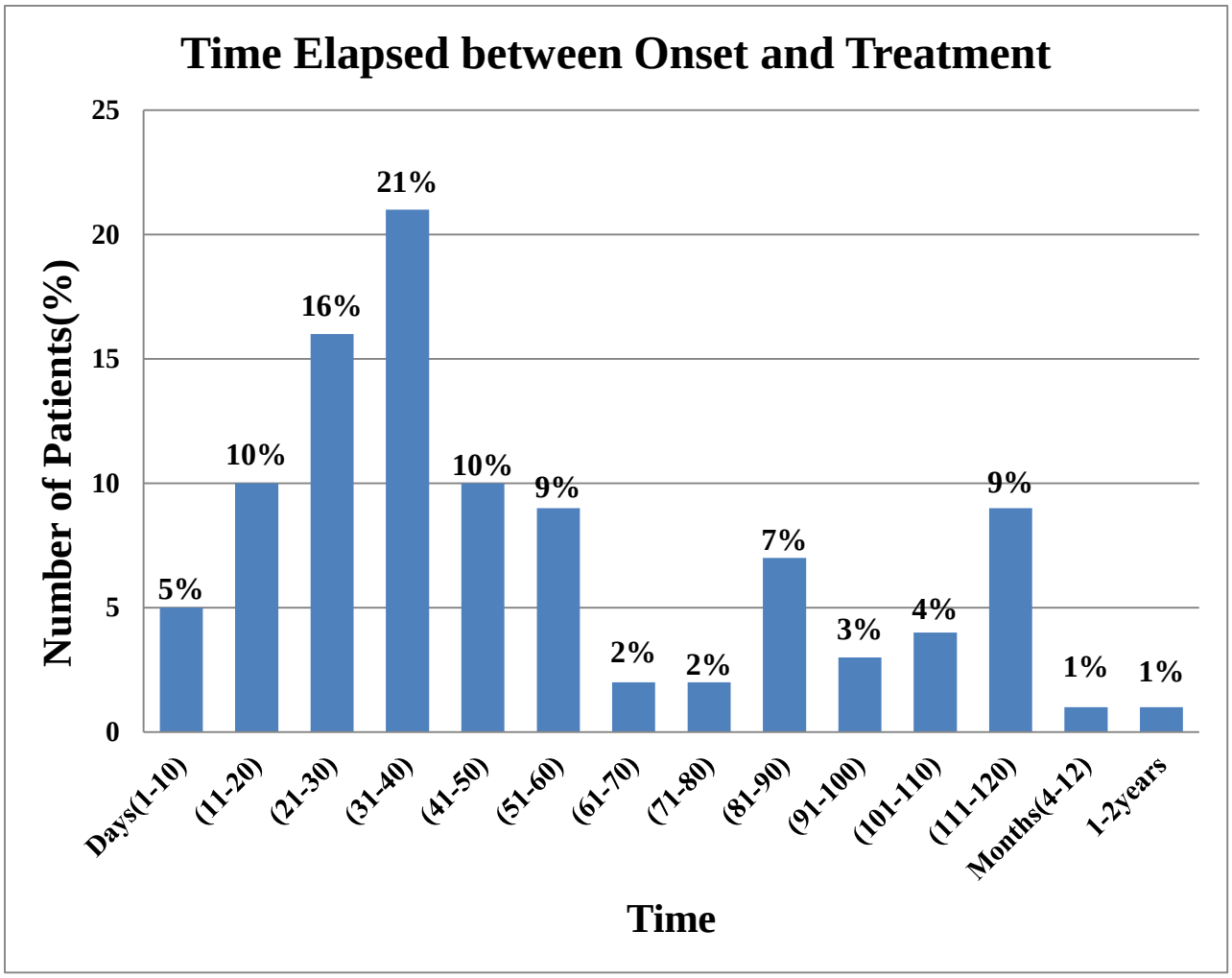

Figure 4.2.2: Time Elapsed between Onset & Treatment

Among 100 patients, majority of patients (21%) took 31-40 days between onset of symptoms & treatment followed by 16% patients took 21-30days whereas minority of patients (2%) took 4months-2years.

4.2.3 Types of TB

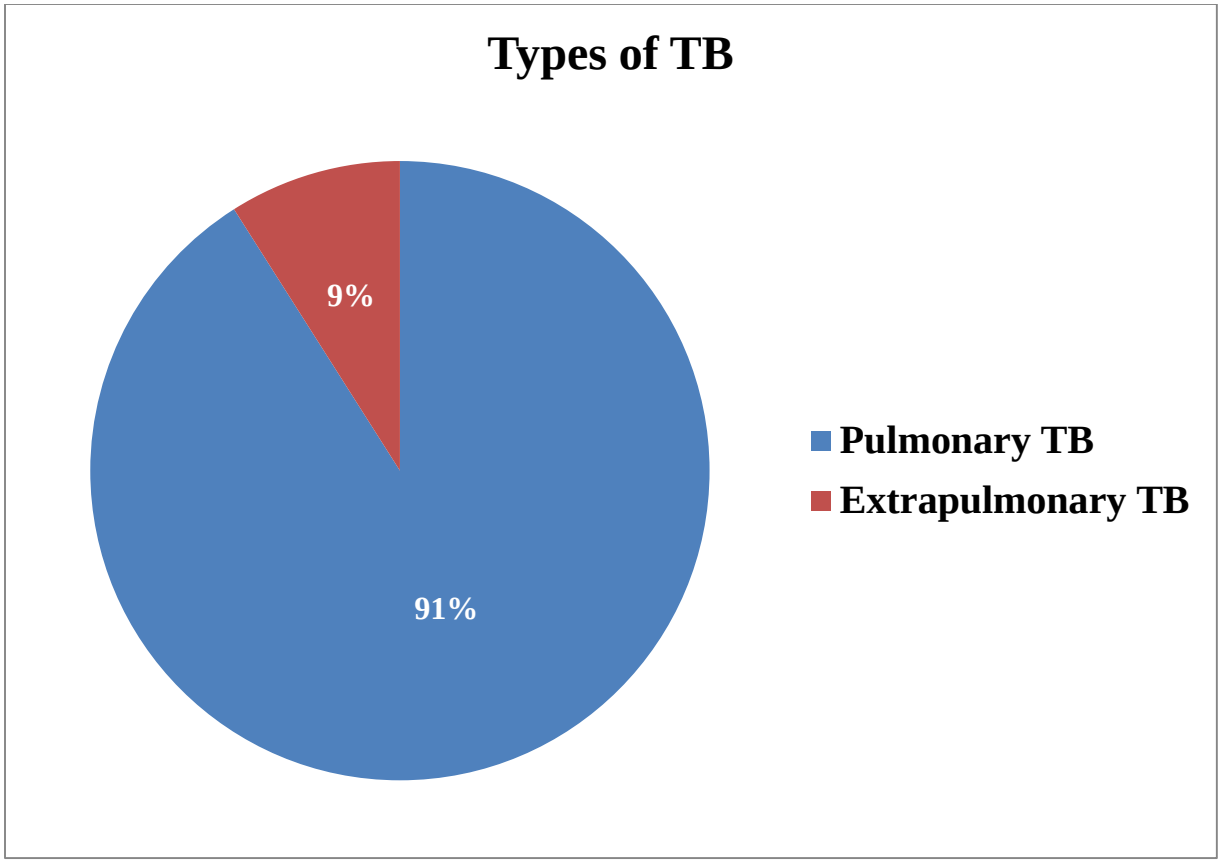

Figure 4.2.3: Types of TB

Among 100 patients, 91% had pulmonary TB and 9% had extrapulmonary TB.

4.2.4 Medications Taken for TB

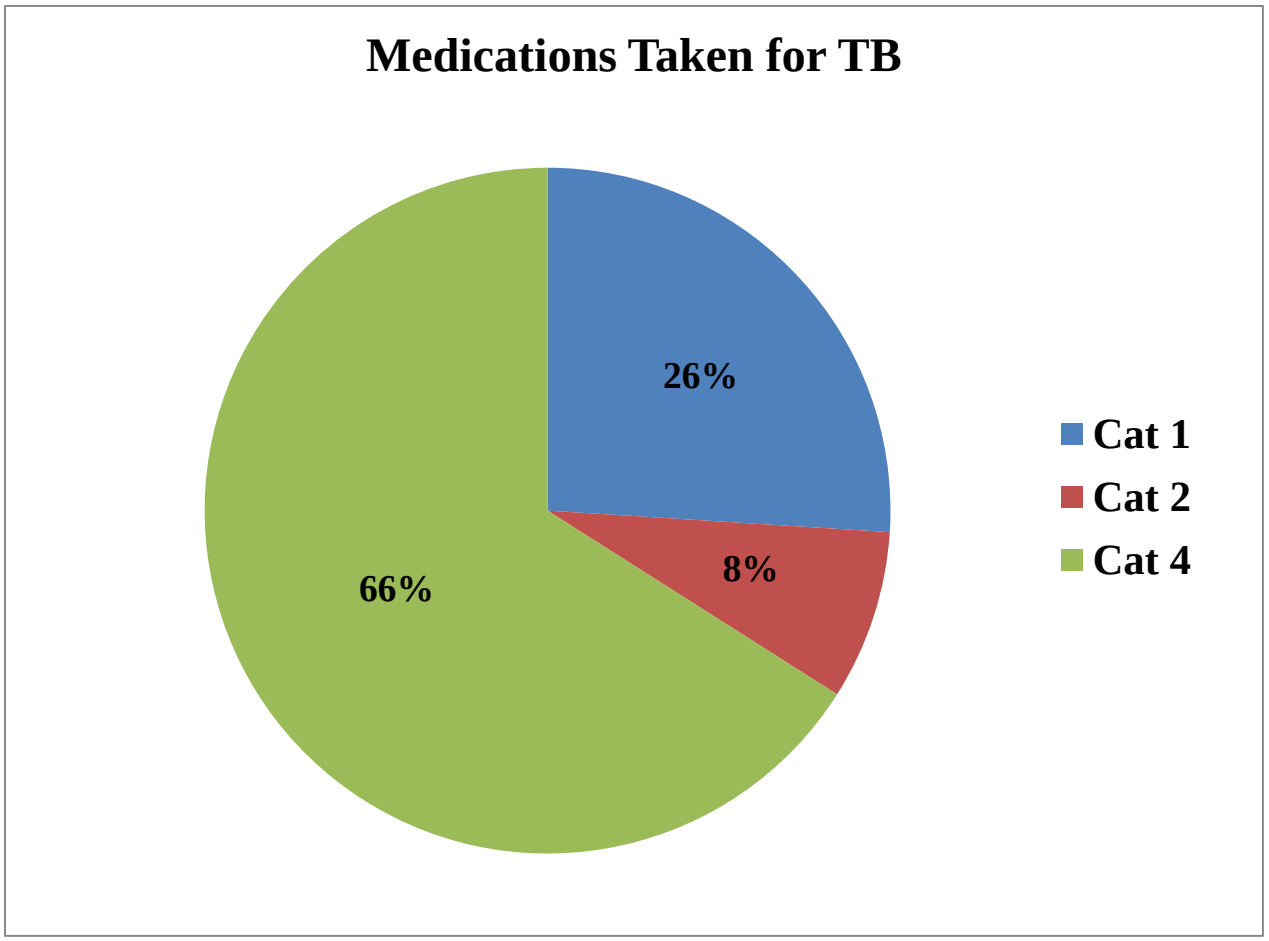

Figure 4.2.4: Medication Taken for TB

Among 100 patients, minority of patients (26%) took Cat 1and majority of patients (66%) took Cat 4 medications for TB.

4.2.5 MDR-TB Incidence

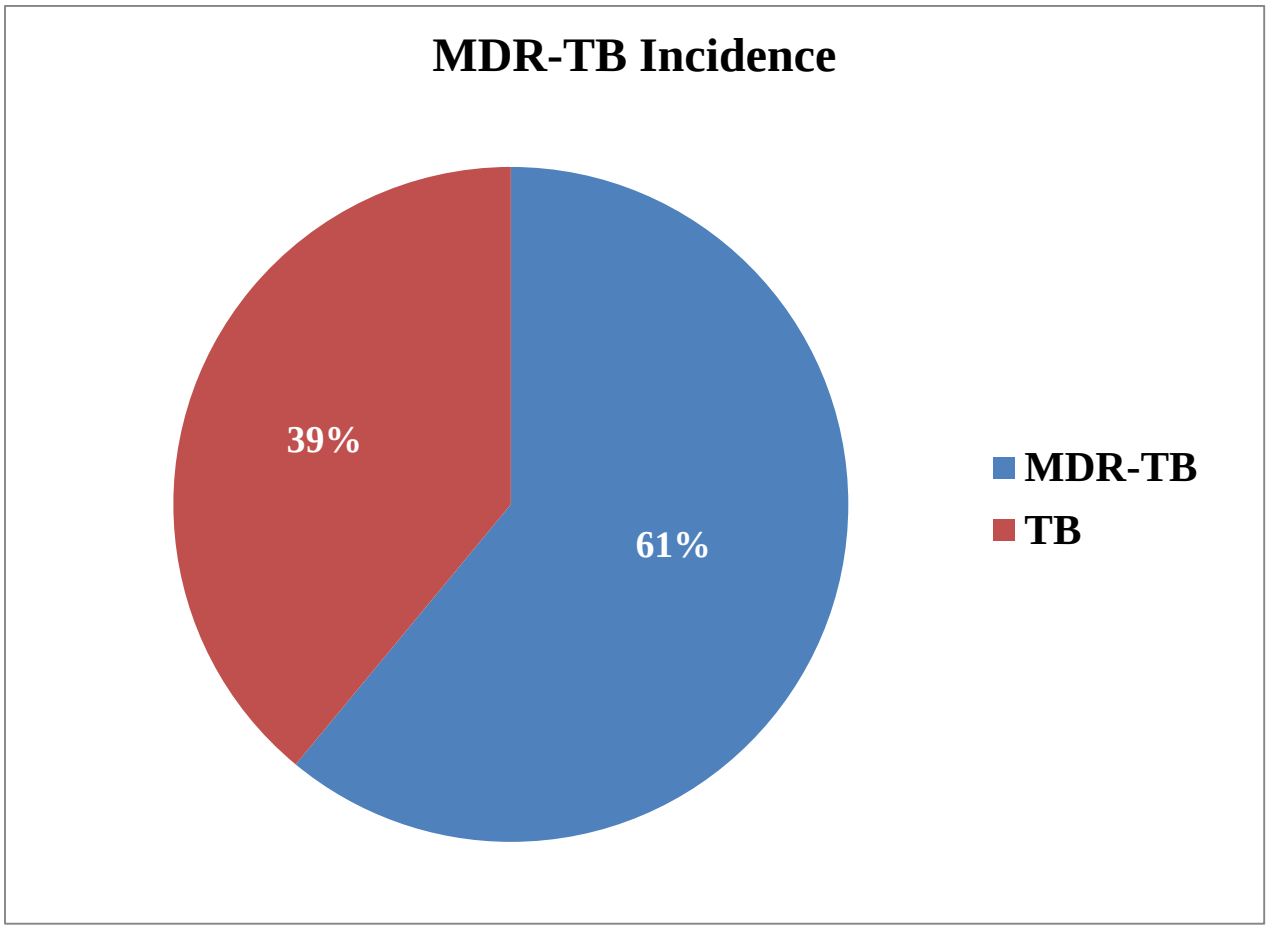

Figure 4.2.5: Incidence of MDR-TB

Among 100 patients, majority of patients (61%) were MDR patient and rest 39% were Non-MDR patient.

4.2.6 Completion of Primary TB Treatment for MDR-TB Patients

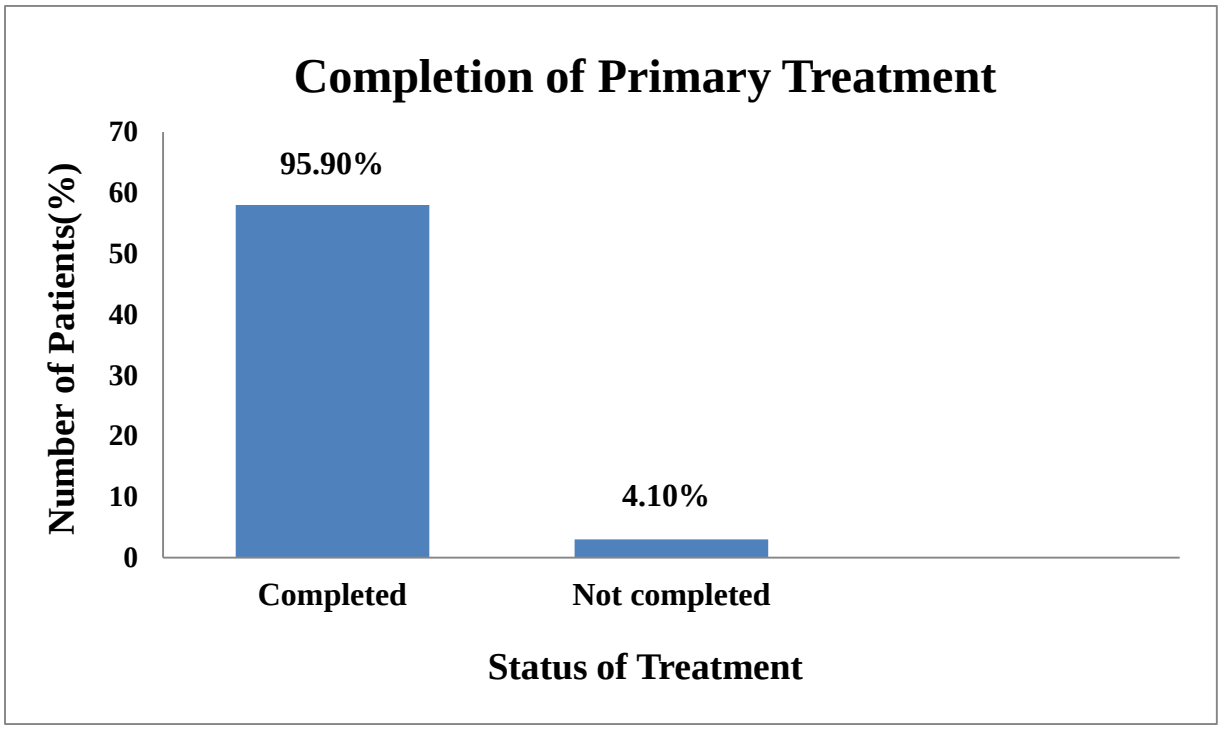

Figure 4.2.6: Completion of Primary TB Treatment for MDR-TB Patients

Among 100 patients, majority of patients (95.90%) had completed their primary treatment and 4.10% had not.

4.2.7 History of Prior TB Treatment

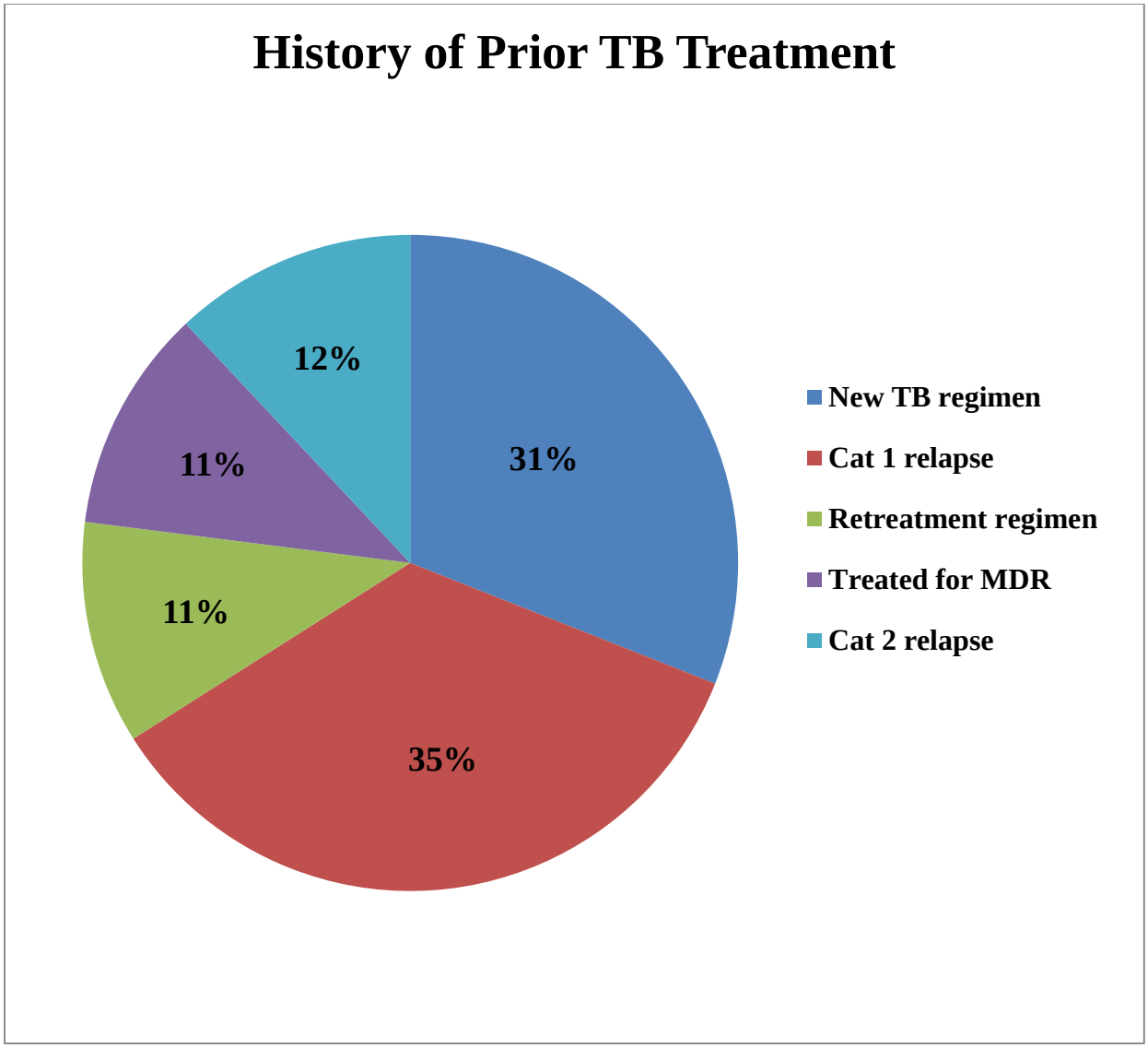

Figure 4.2.7: History of Prior TB Treatment

In our study, we found that 35% patients are treated for TB due to Cat I relapse, 12% patients are treated due to Cat II relapse and 31% patients are treated for new TB regimen.

4.3 Parameters of DM

4.3.1 Prevalence of DM

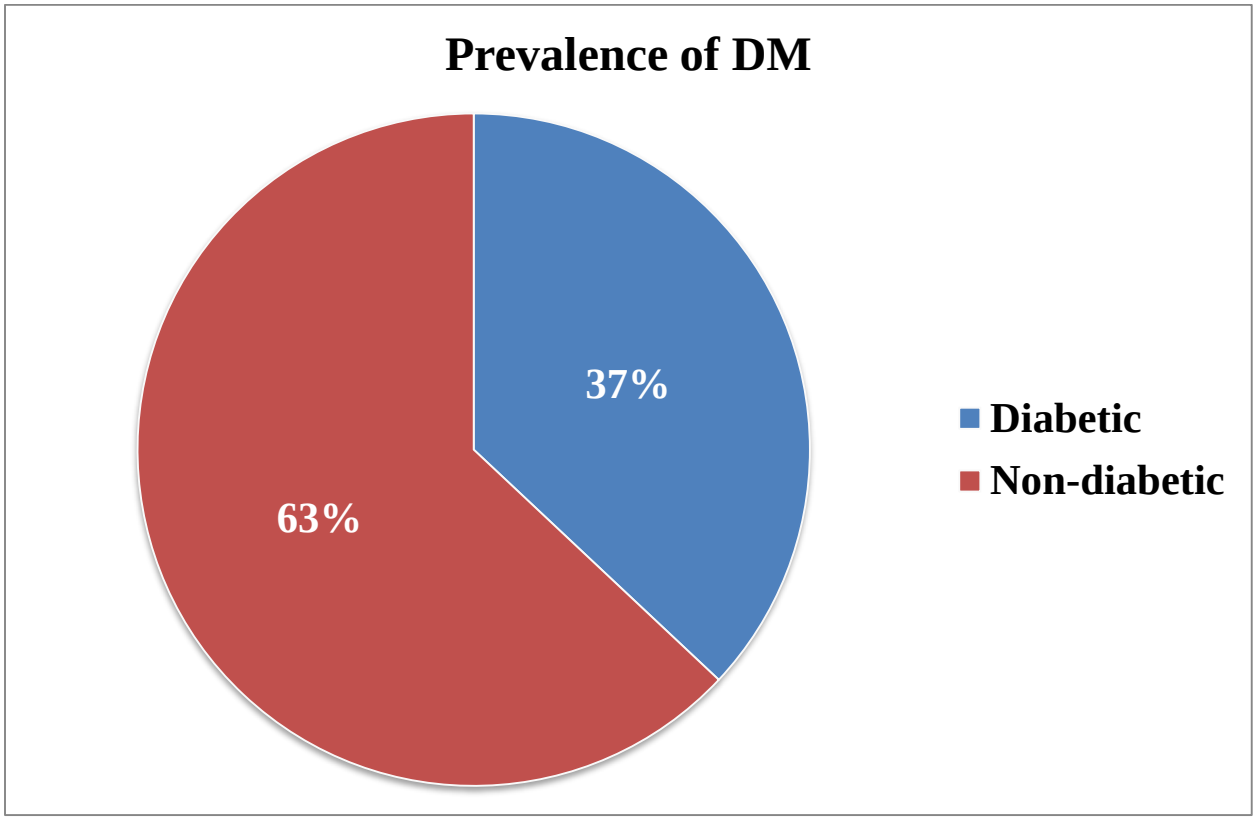

Figure 4.3.1: Prevalence of DM

In our study, majority of patients (63%) were Non-diabetic and 37% were Diabetic.

4.3.2 Types of DM

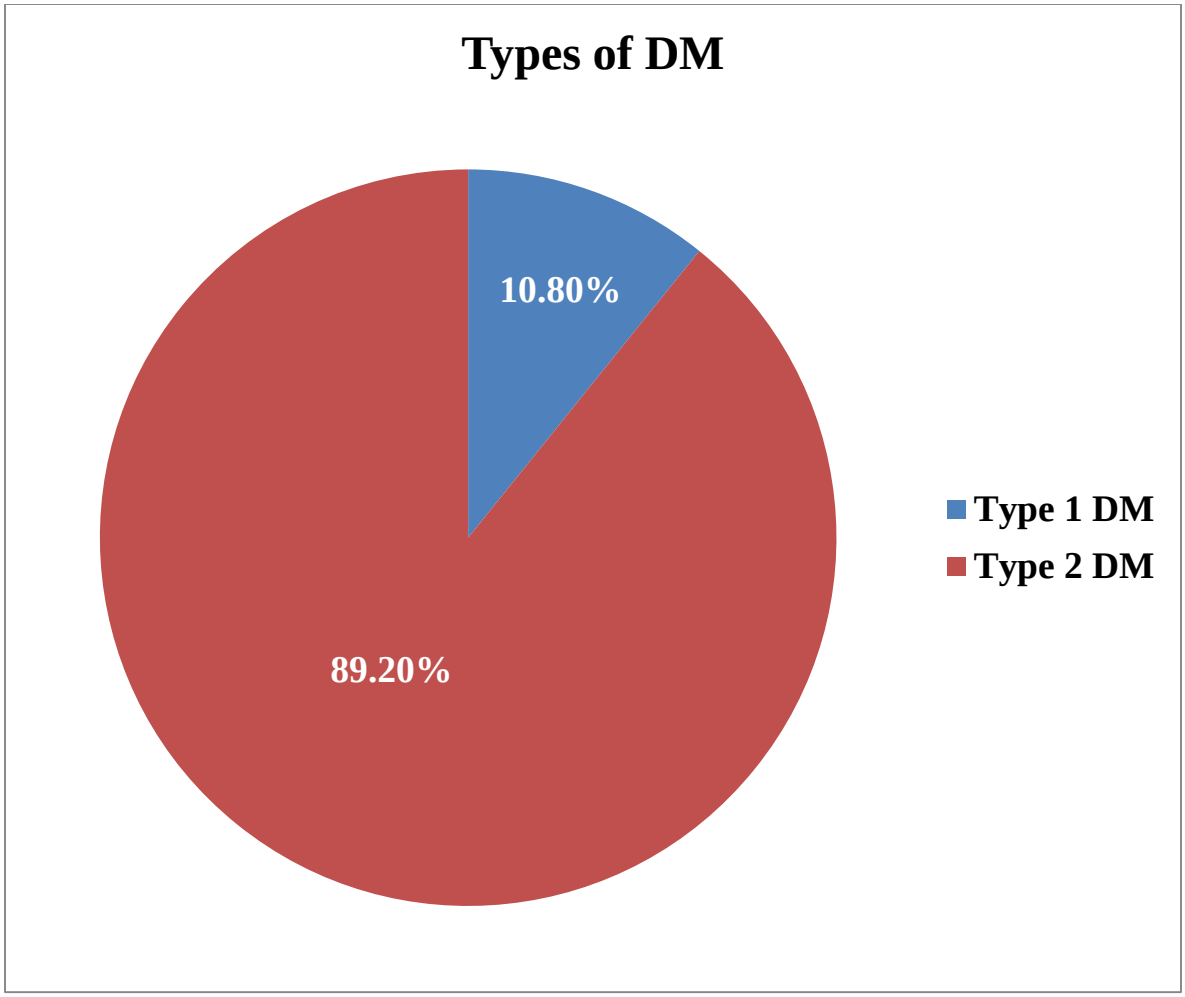

Figure 4.3.2: Types of DM

Among 100 patients, 10.80% had type 1diabetes and 89.20% had type 2 diabetes.

4.3.3: Duration of Diabetes

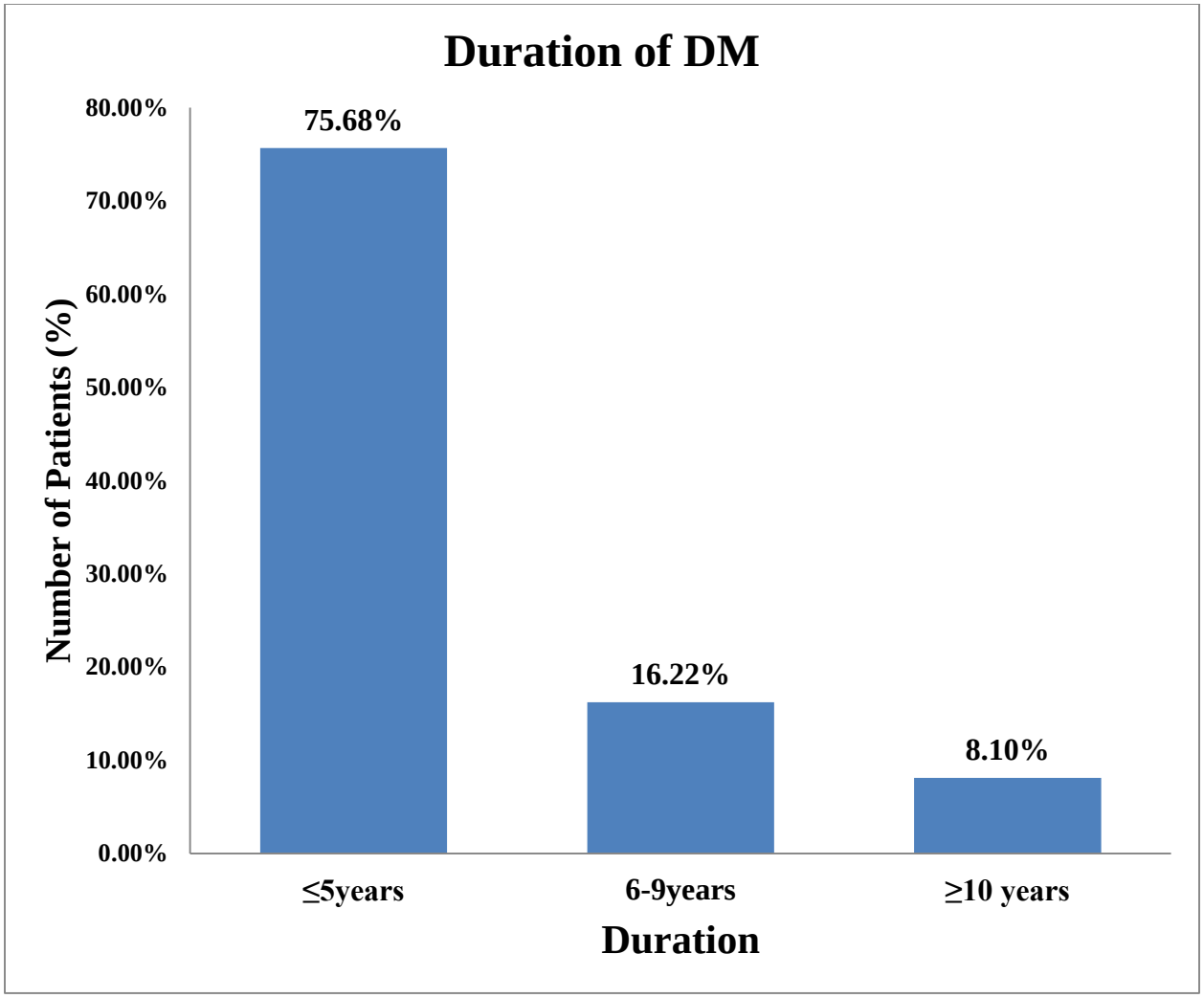

Figure 4.3.3: Duration of DM

Among 100 patients, majority of patients (75.68%) had diabetes for ≤5years,16.22% had diabetes for 6-9 years and minority of patients (8.10%) had diabetes for ≥10years.

4.3.4: Medications Taken for DM

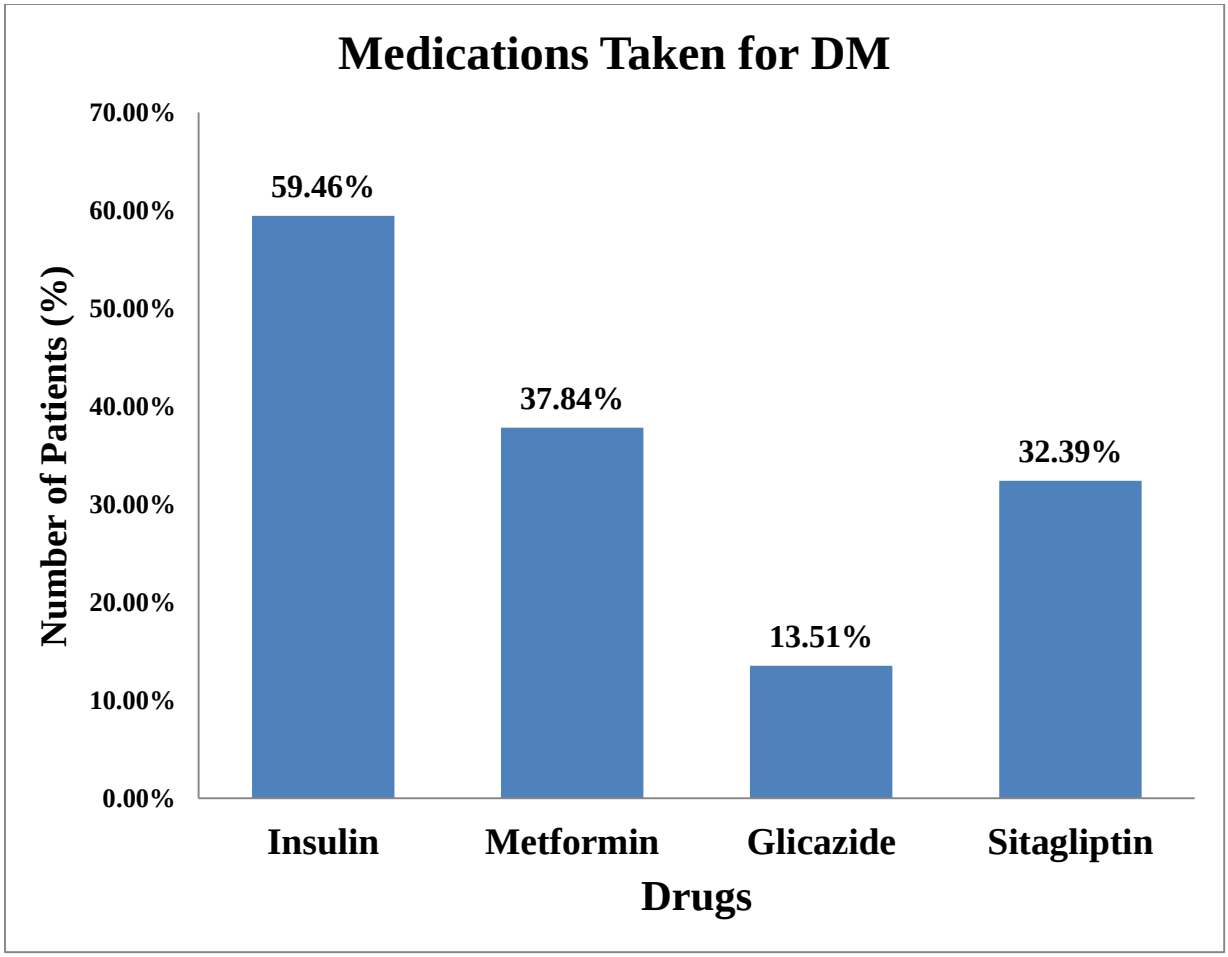

Figure 4.3.4: Medications Taken for DM

Among 100 patients, majority of patients (59.46%) had taken Insulin and minority of patients (13.51%) had taken Glicazide.

4.3.5 Family History of DM

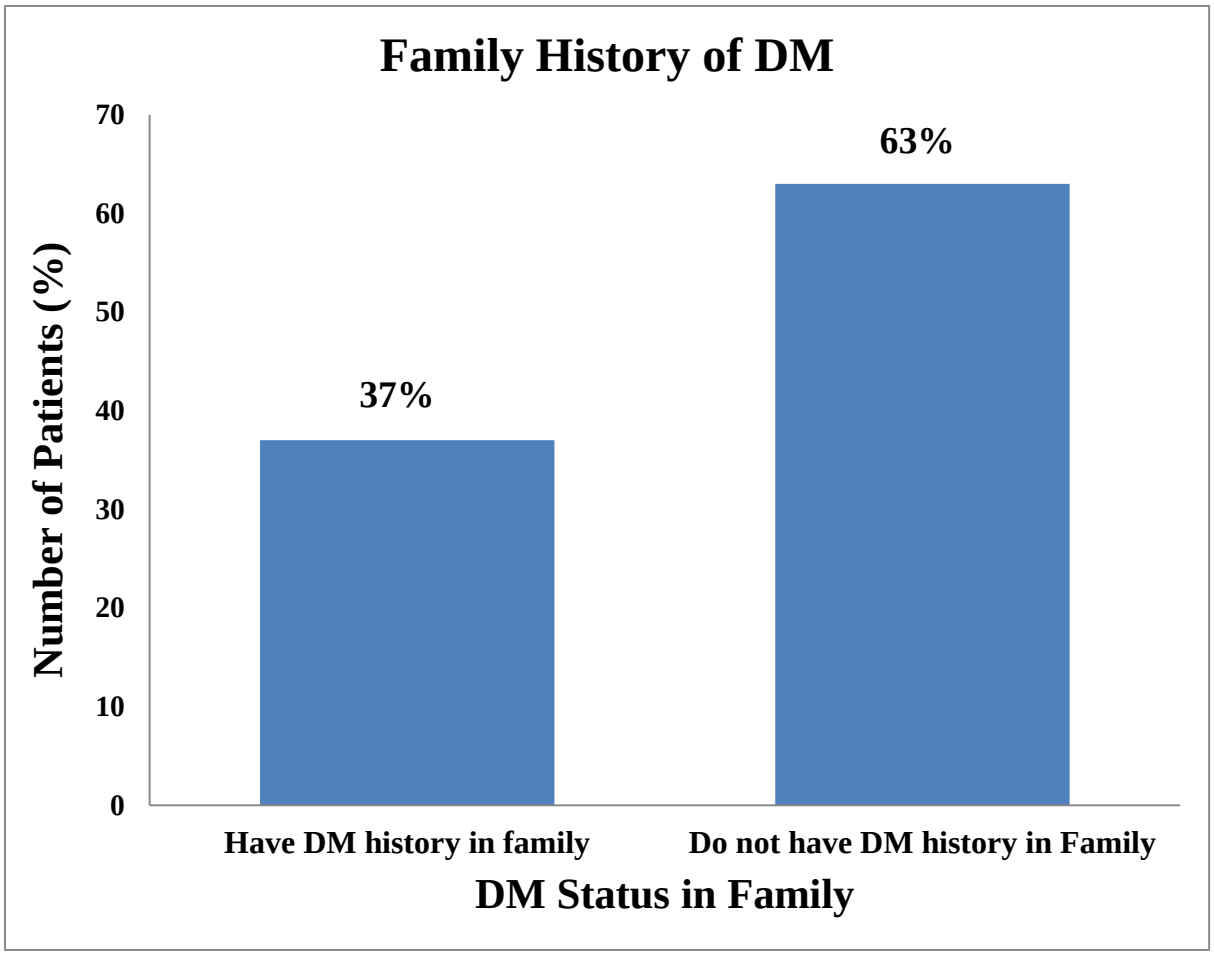

Figure 4.3.5: Family History of DM

Among 100 patients,37% people had family history of DM and 63% didn't have.

4.3.6 Symptoms of Hyperglycemia

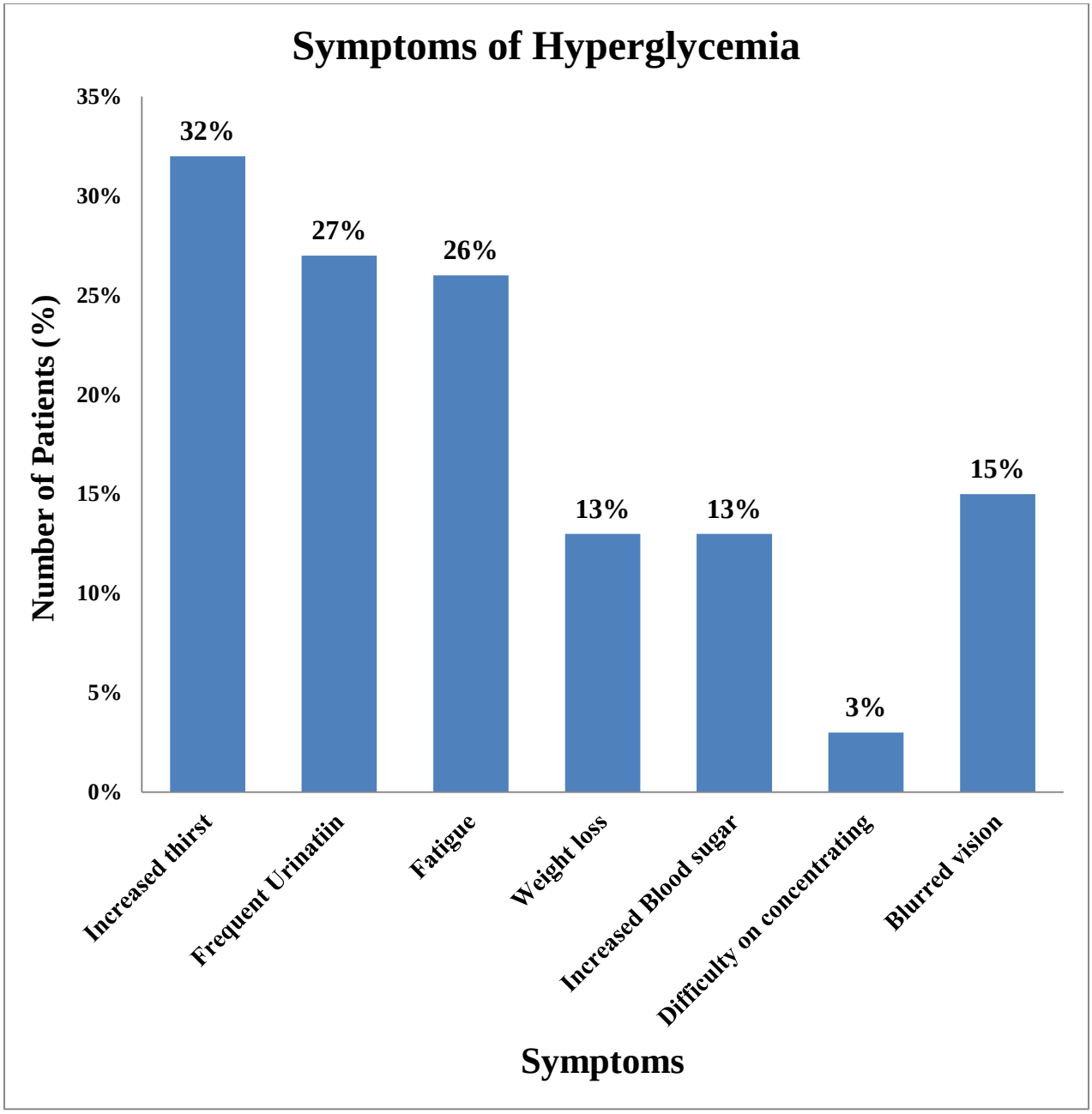

Figure 4.3.6: Symptoms of Hyperglycemia

Among 100 patients, majority of patients (32%) had Increased thirst followed by frequent urination (27%) and fatigue (26%) and minority of patients (3%) had difficulty on concentrating.

4.3.7 Frequency of Meeting Doctor

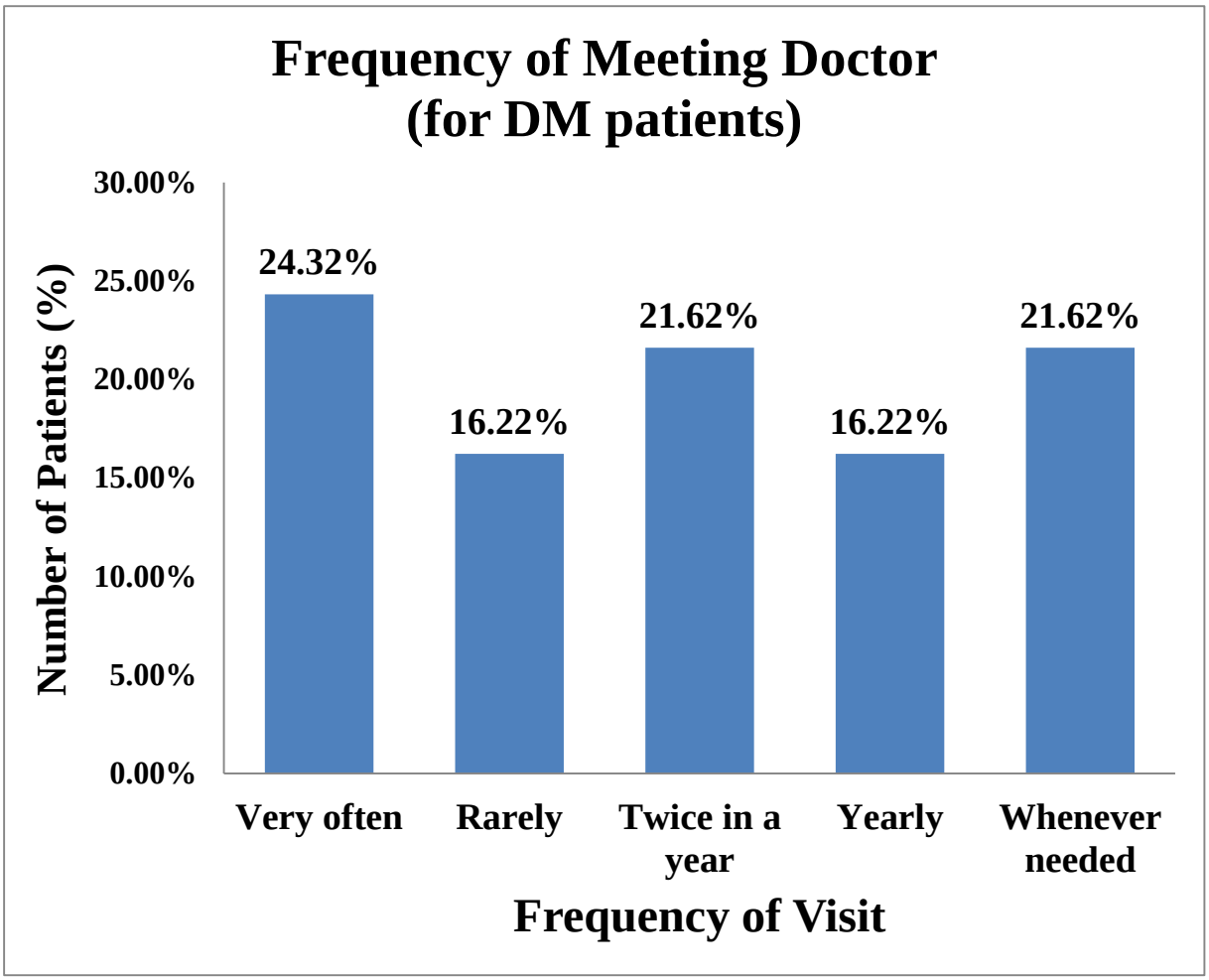

Figure 4.3.7: Frequency of Meeting Doctor

Among 100 patients, majority of patients (24.32%) very often consulted doctor and minority of patients (16.22%) rarely or yearly consulted doctor in a year,16.22% consulted doctor yearly and 21.62% consulted doctor whenever needed.

4.3.8 Mode of Action for Non-Diabetic Patients If Diabetes Suspected

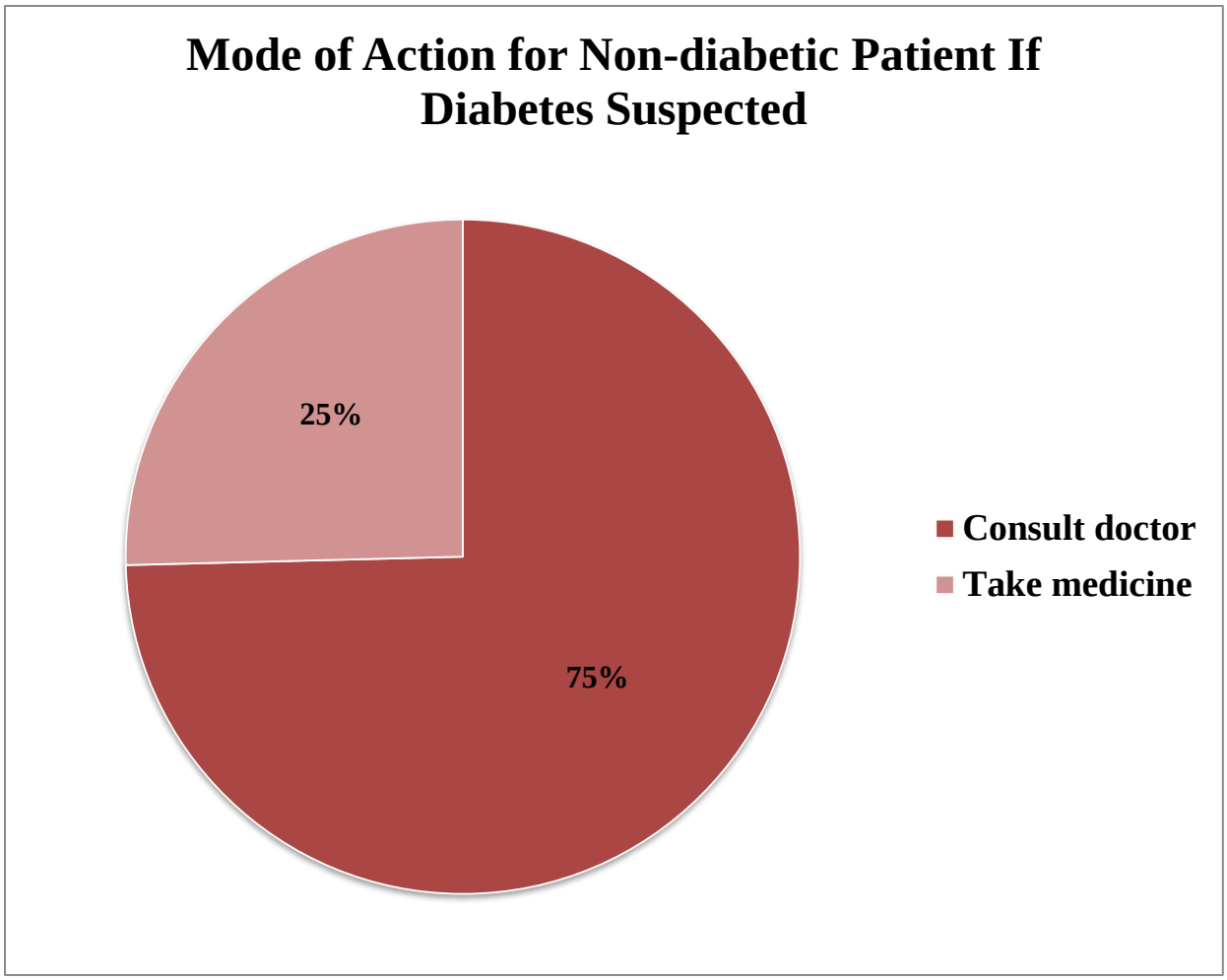

Figure 4.3.8: Mode of Action for Non-Diabetic Patients If Diabetes Suspected

Among 100 patients,75% would consult doctor and 25% would take medicine.

4.3.9 Knowledge of TB Increasing Chances of Diabetes

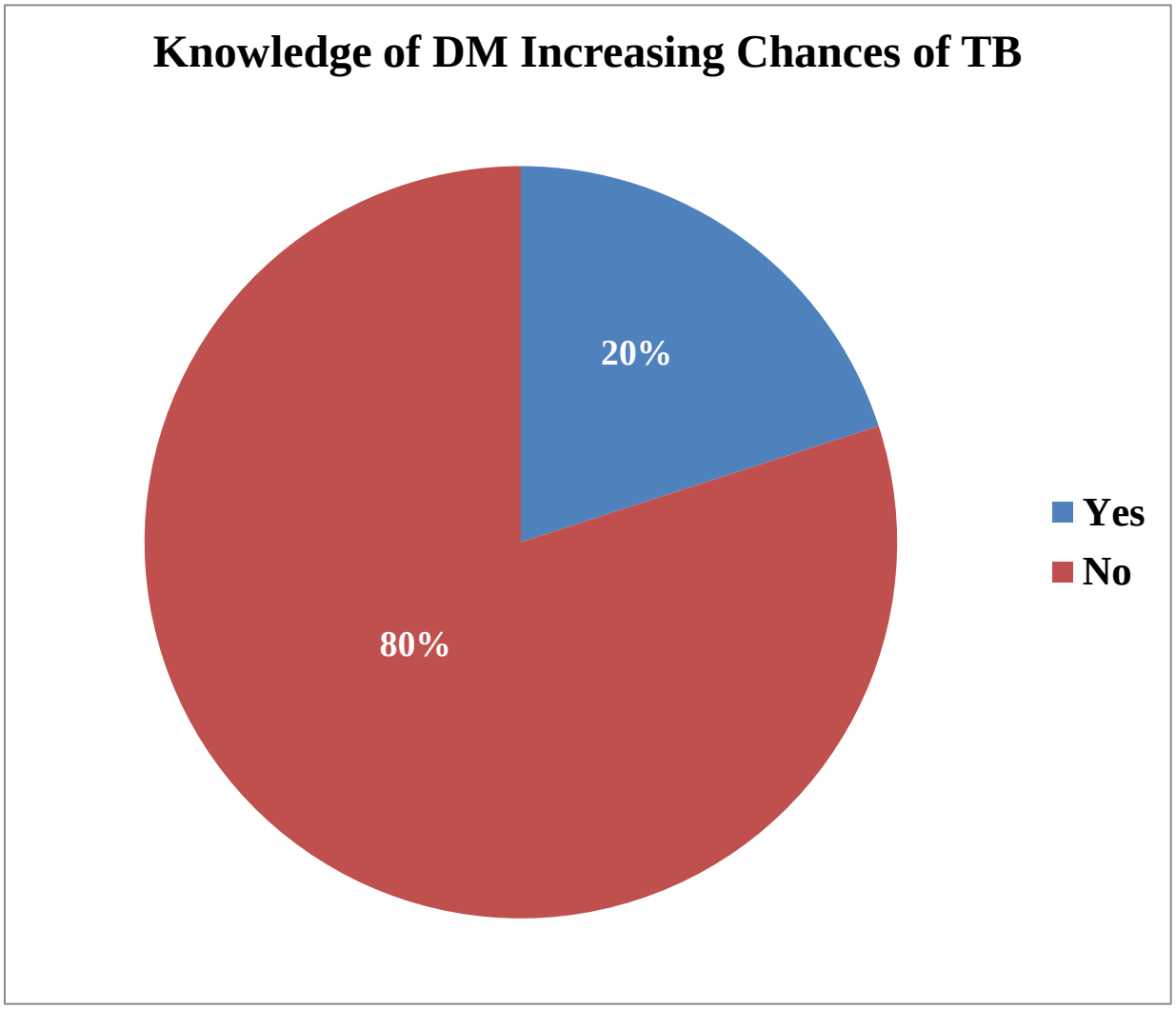

Figure 4.3.9: Knowledge of TB Increasing Chances of Diabetes

Among 100 patients,20% had known that DM increases chance of TB and 80% didn't know.

4.3.10: Control of Blood Sugar Level of Diabetic Patients after Diagnosis with TB

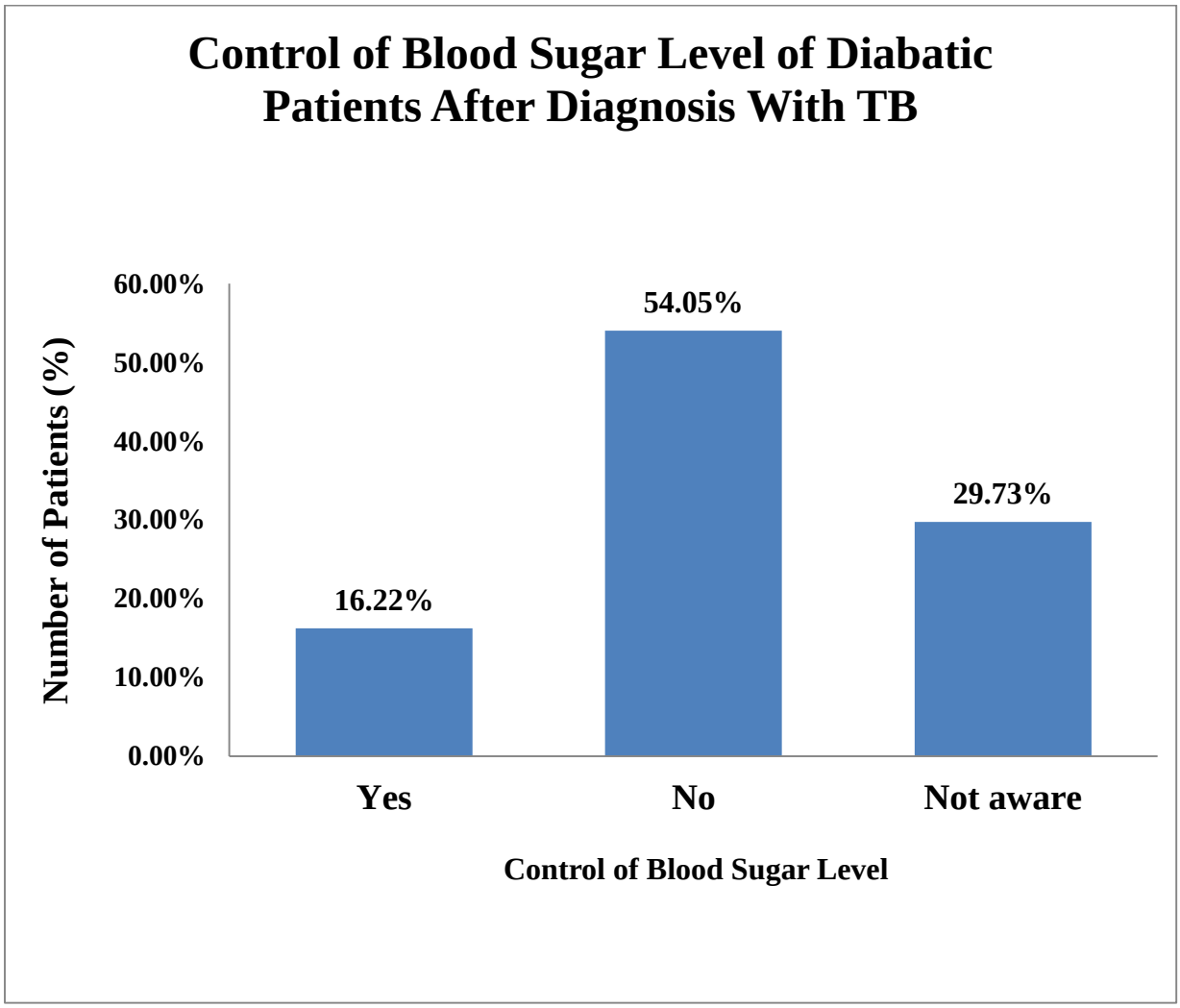

Figure 4.3.10: Control of Blood Sugar Level of Diabetic Patients after Diagnosis with TB

After diagnosis, majority of patients (54.05%) had uncontrolled blood level and minority of patients (16.22%) had controlled blood level.

4.4 Association of Factors Contributing to DM Prevalence in TB & MDR-TB Patients

4.4.1 Proportion of TB & MDR-TB patients having DM

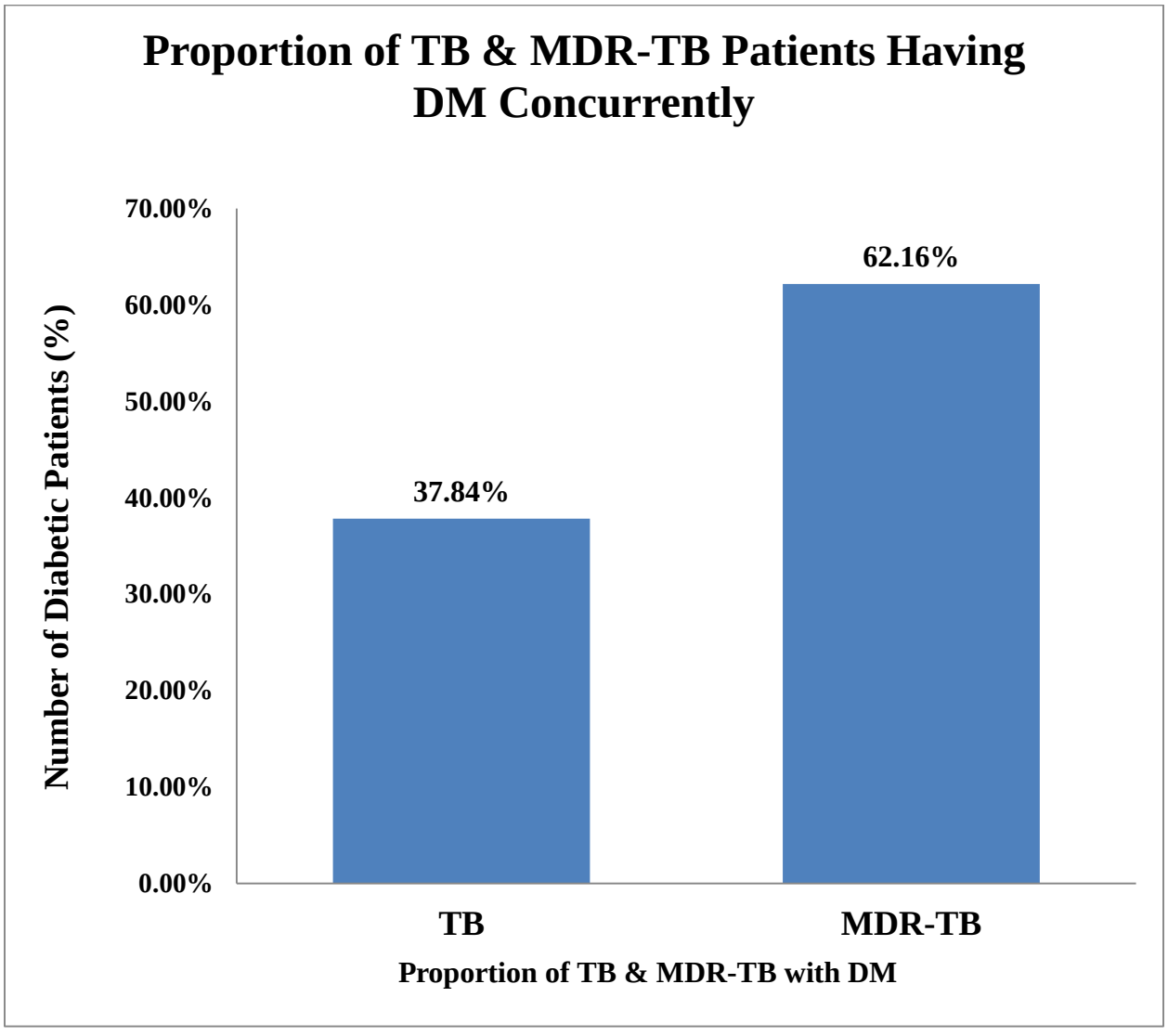

Figure 4.4.1: Proportion of TB & MDR-TB patients having DM

The sample of 100 patients showed that 37.84% of the TB patients had diabetes whereas 62.16% of MDR-TB patients had diabetes.

4.4.2 Prevalence of DM in Male & Female TB Patients

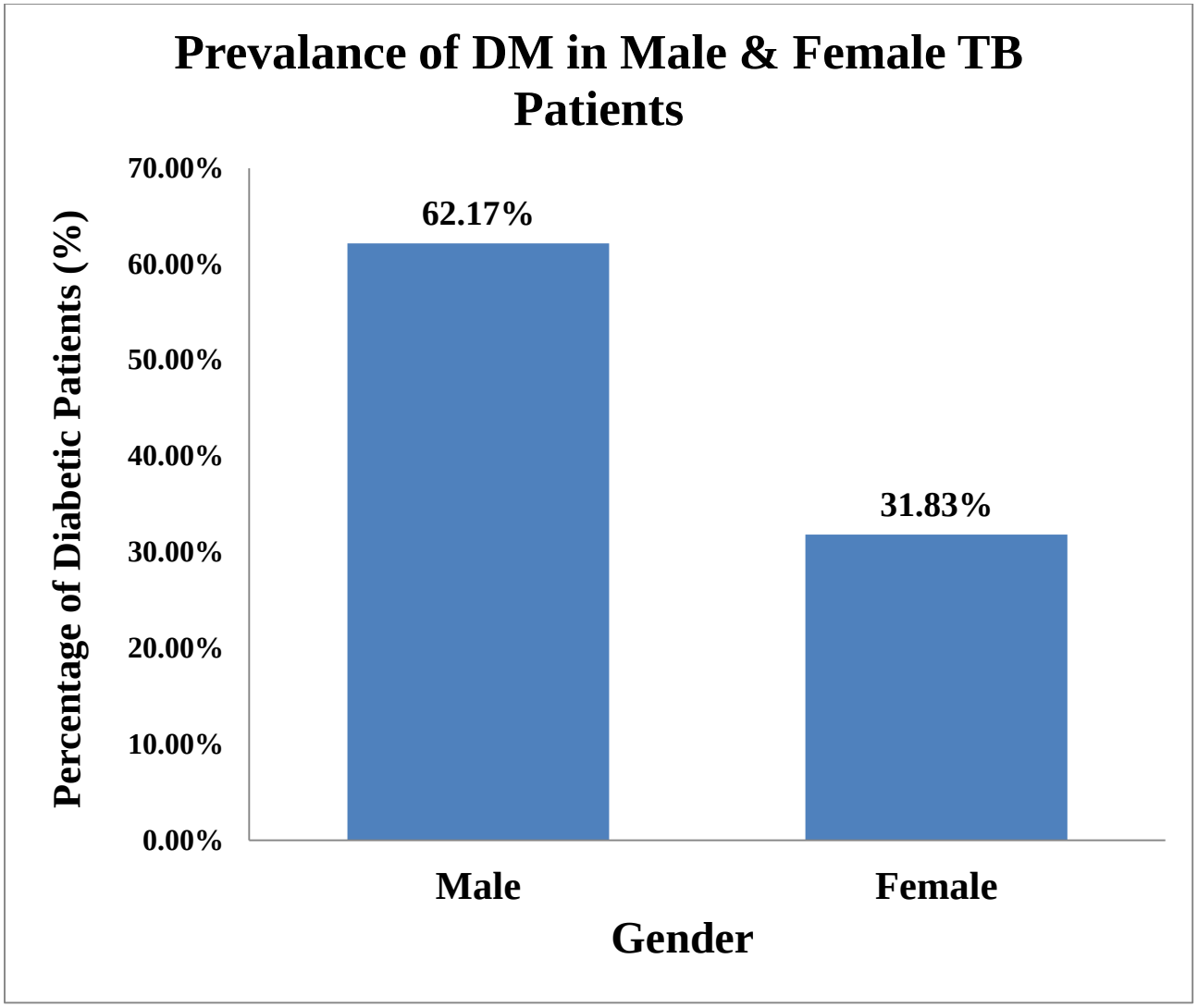

Figure 4.4.2: Prevalence of DM in Male & Female TB

The sample of 100 patients showed that 62.17% of the TB patients were male whereas 31.83% of TB patients were female.

4.4.3: Prevalence of DM in the different Age Groups

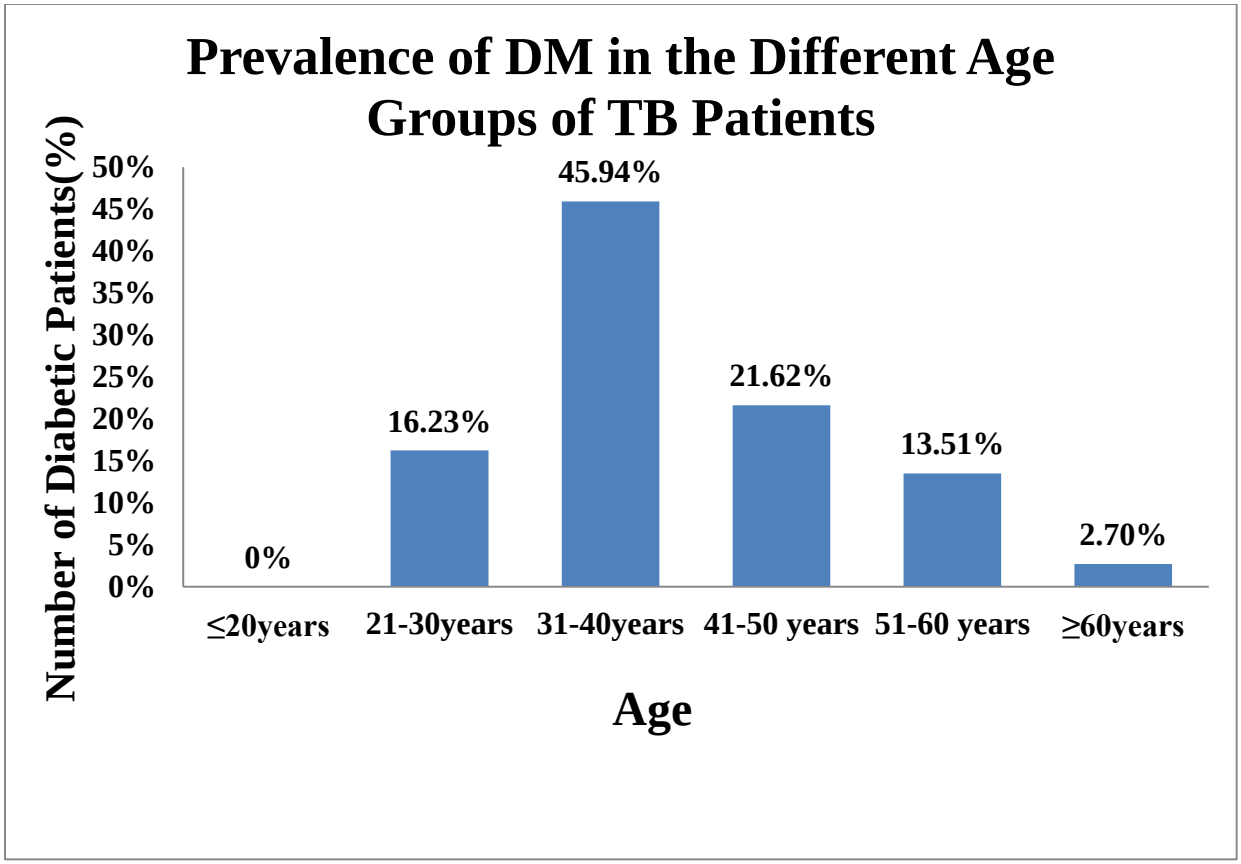

Figure 4.4.2: Prevalence of DM in Male & Female TB Patients

The sample of 100 patients showed that majority of the TB patients(45.94%)who had DM were 31-40 years of age whereas minority of TB patients(2.70%) having DM were ≥60years of age.

4.4.4 Prevalence of DM in TB patients with Different Education Backgrounds

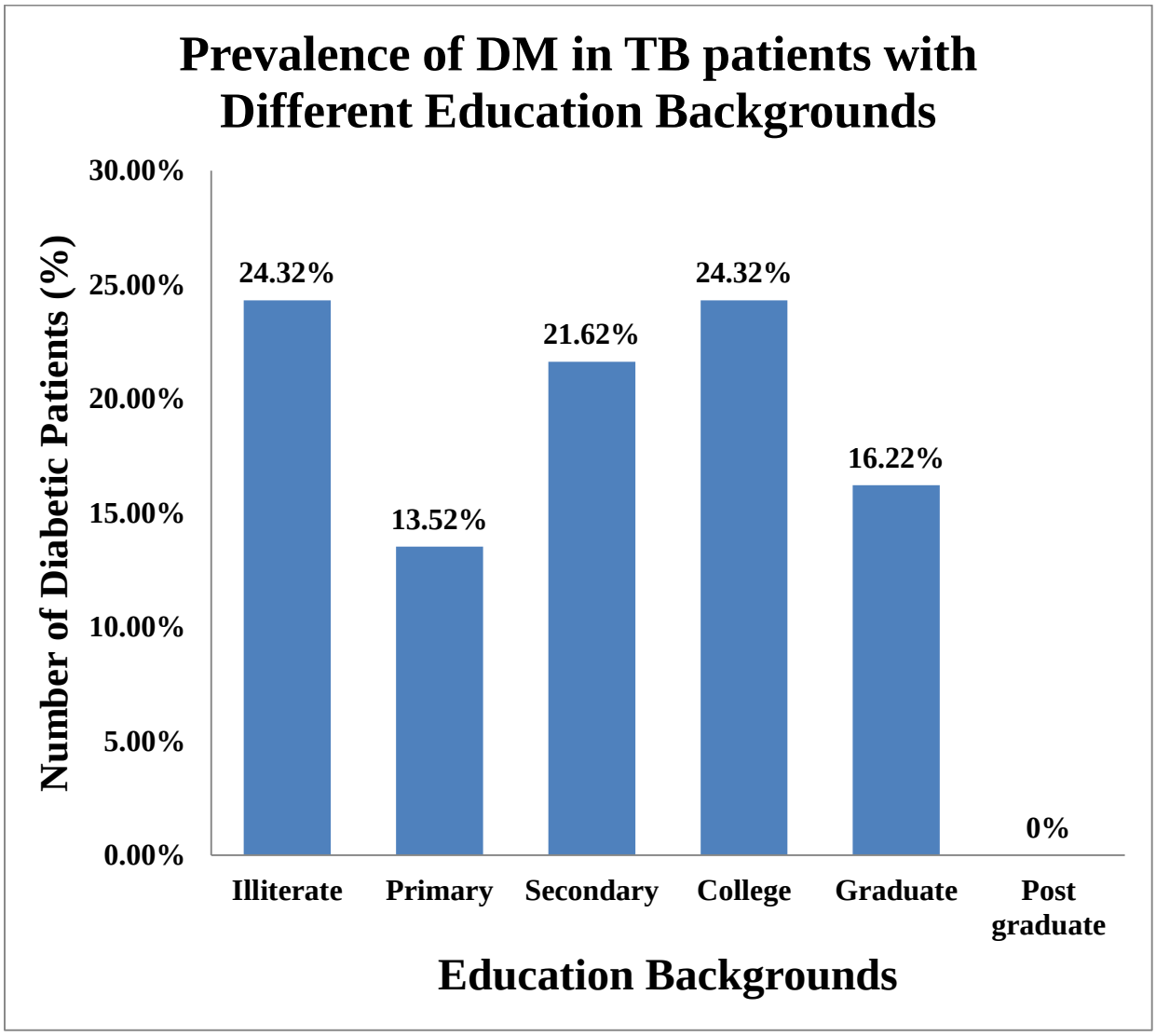

Figure 4.4.4: Prevalence of DM in TB patients with Different Education Backgrounds

The sample of 100 patients showed that majority of TB patients having DM (24.32%) were illiterate or from college whereas minority of TB patients having DM(13.52%) were from primary education.

4.4.5 DM Occurrence with Relation to Previous Diagnosis with TB

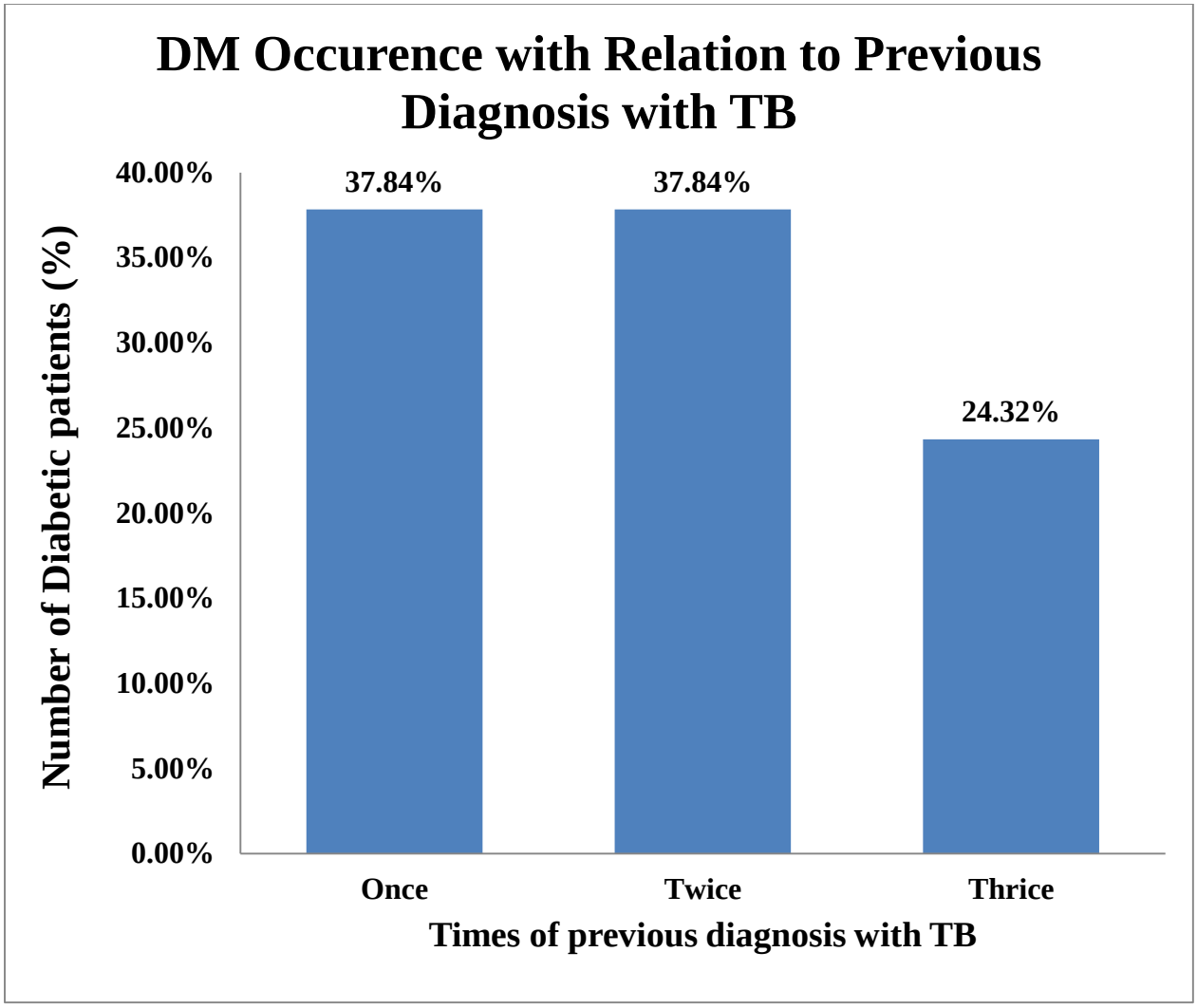

Figure 4.4.5: DM Occurrence with Relation to Previous Diagnosis with TB

The sample of 100 patients showed that majority of TB patients having DM (37.84%) were previously diagnosed with TB once or twice whereas minority of TB patients having DM (24.32%) were previously diagnosed with TB thrice.

4.4.6: DM Occurrence with relation to Time Elapsed between Onset & Treatment of TB

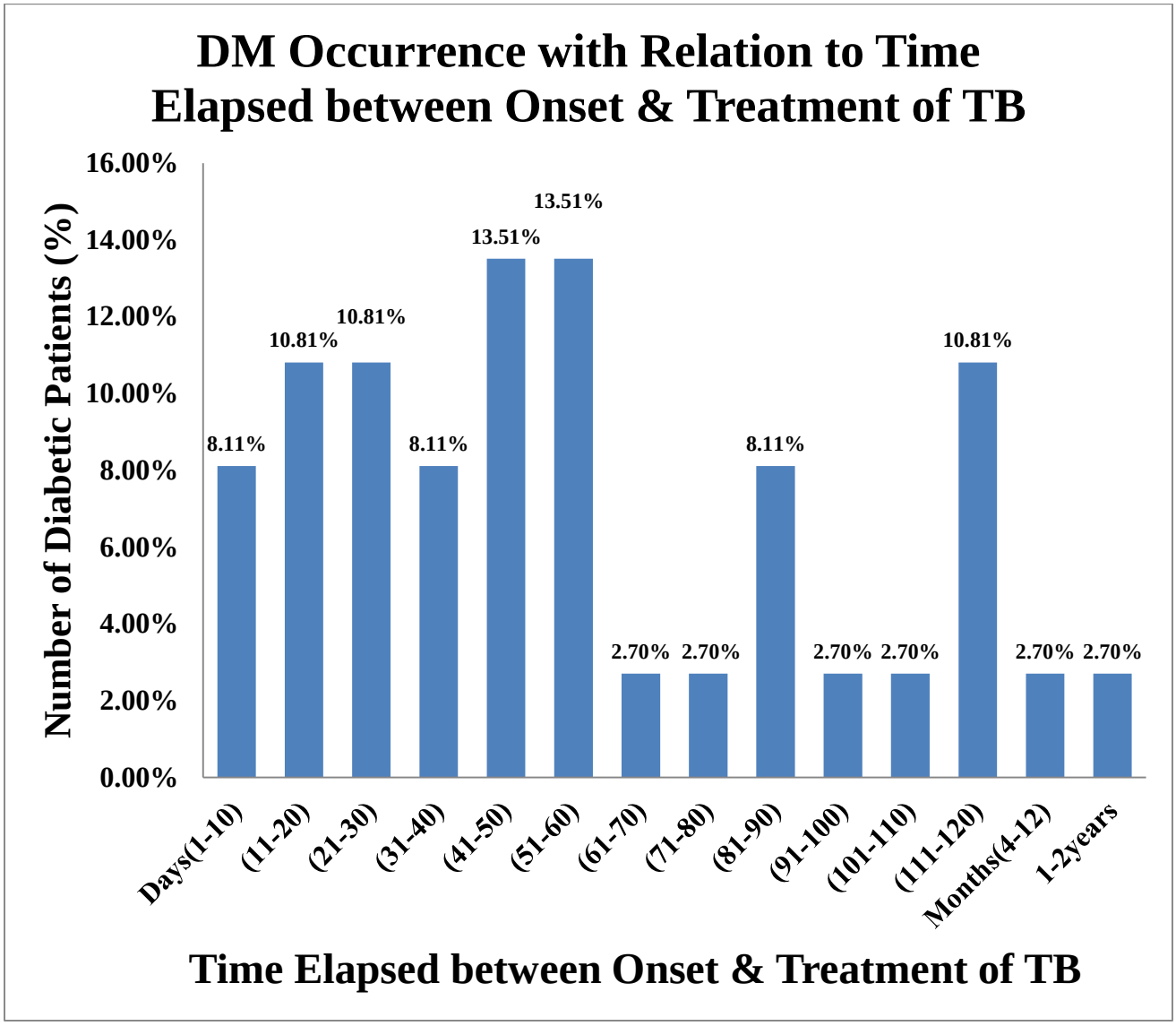

Figure 4.4.6: DM Occurrence with relation to Time Elapsed between Onset & Treatment of TB

The sample of 100 patients showed that majority of TB patients having DM (13.51%) took (41-50 days) or (51-60 days) between onset of symptom & tratment of TB whereas minority of TB patients having DM (2.70%) took (61-70days) or (71-80days) or (91-100days)or (101-110days) or (4-12months) or (1-2years).

4.4.7 Prevalence of DM According to Family History of DM

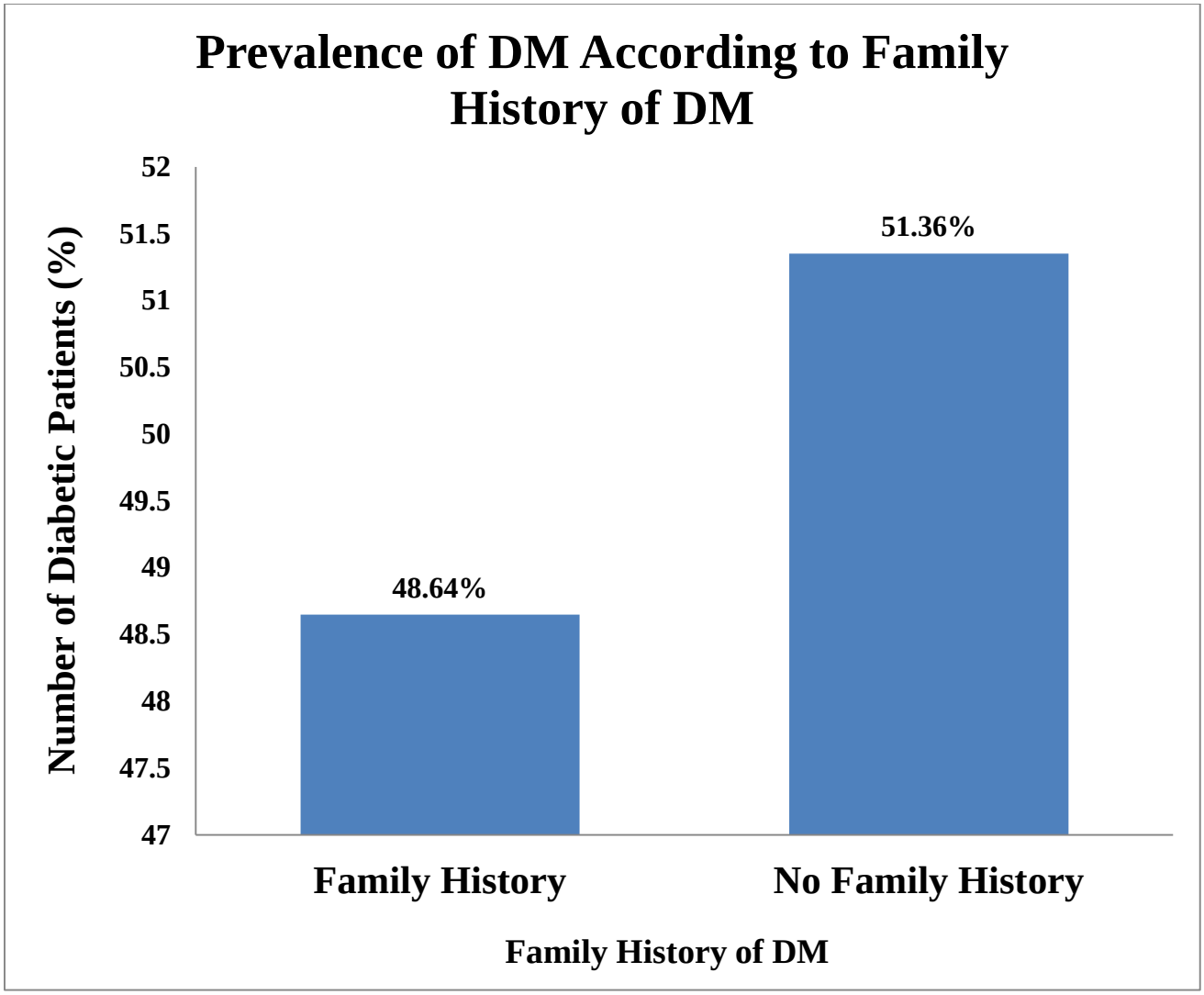

Figure 4.4.7: Prevalence of DM According to Family History of DM

The sample of 100 patients showed that majority of TB patients having DM (51.36%) had no family history of DM whereas rest of TB patients having DM (48.64%) had family history of DM.

4.4.8 DM Occurrence with Relation to History of TB Treatment

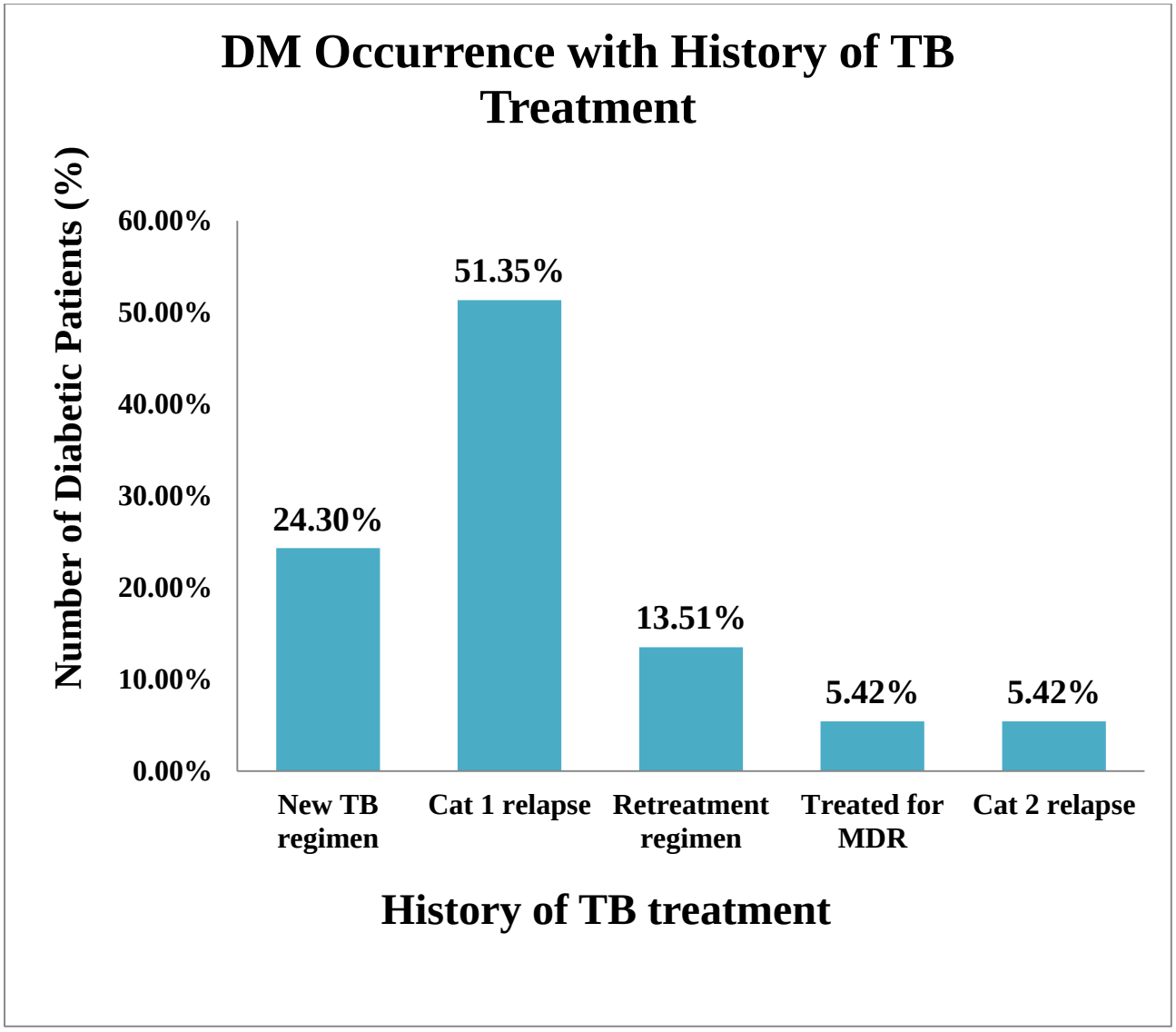

Figure 4.4.8: DM Occurrence with Relation to History of TB Treatment

The sample of 100 patients showed that majority of TB patients having DM (51.35%) had Cat 1 relapse whereas minority of TB patients having DM (5.42%) were treated for MDR or had Cat 2 relapse.

4.4.9 Prevalence of HIV in Diabetic Patients

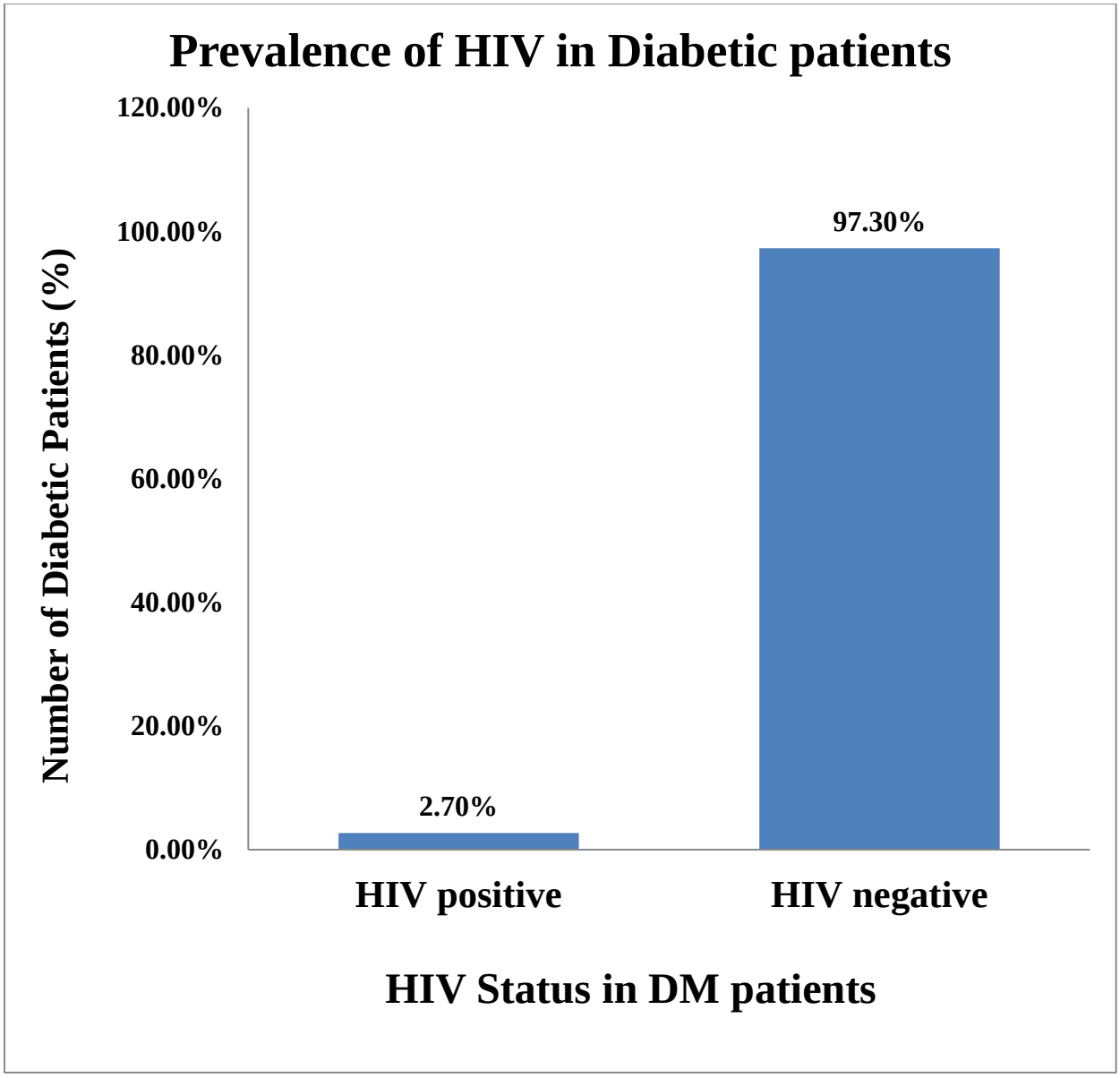

Figure 4.4.9: Prevalence of HIV in Diabetic Patients

The sample of 100 patients showed that 2.70% of the TB patients having diabetes were HIV positive whereas 97.30% TB patients having diabetes were HIV negative.

4.4.10 DM Occurrence in TB patients with Drinking Habits

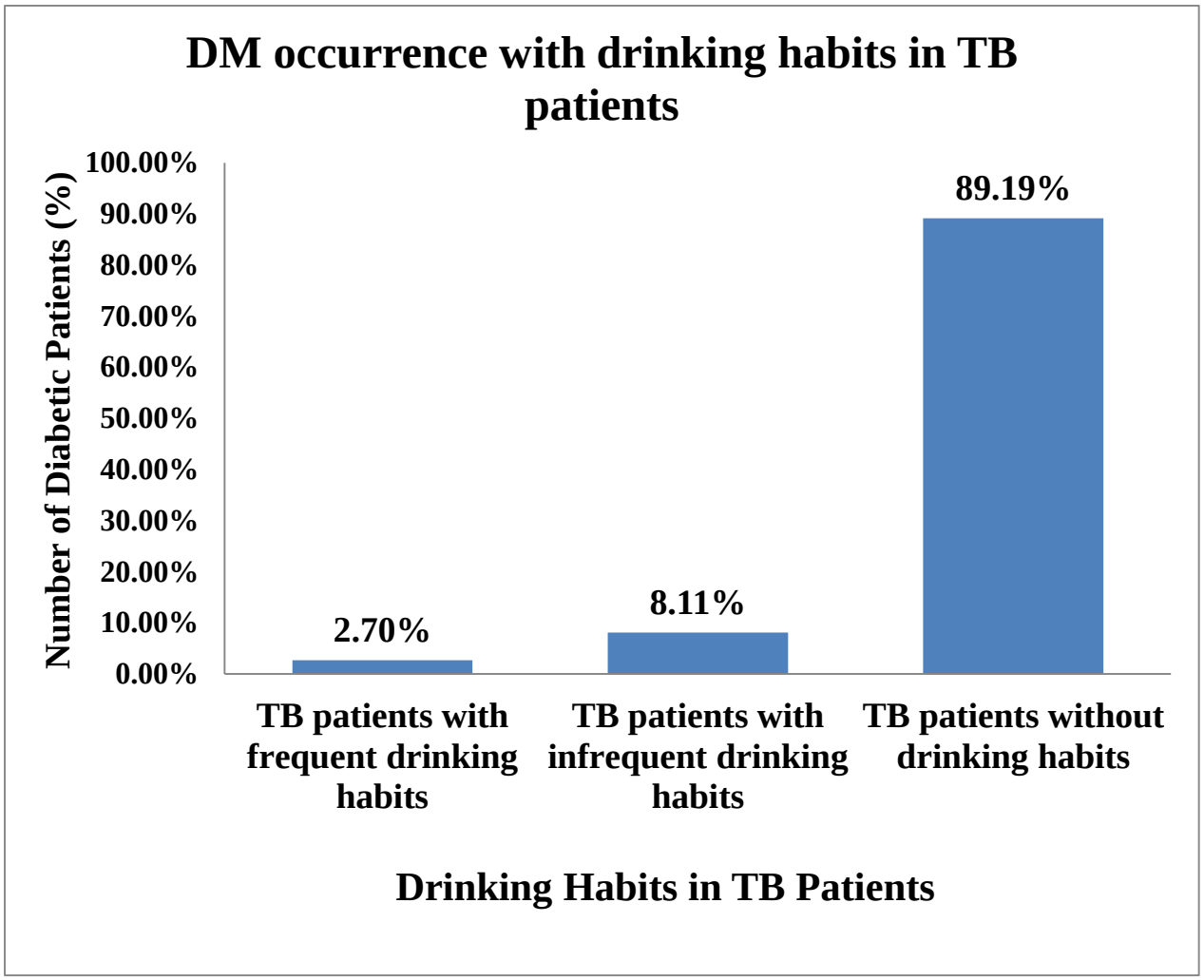

Figure 4.4.10: DM Occurrence in TB patients with Drinking Habits

The sample of 100 patients showed that majority of TB patients having DM (89.19%) had no drinking habits whereas 2.70% TB patients having DM had frequent drinking habits.

4.4.11 DM Occurrence in TB Patients with Smoking Habits

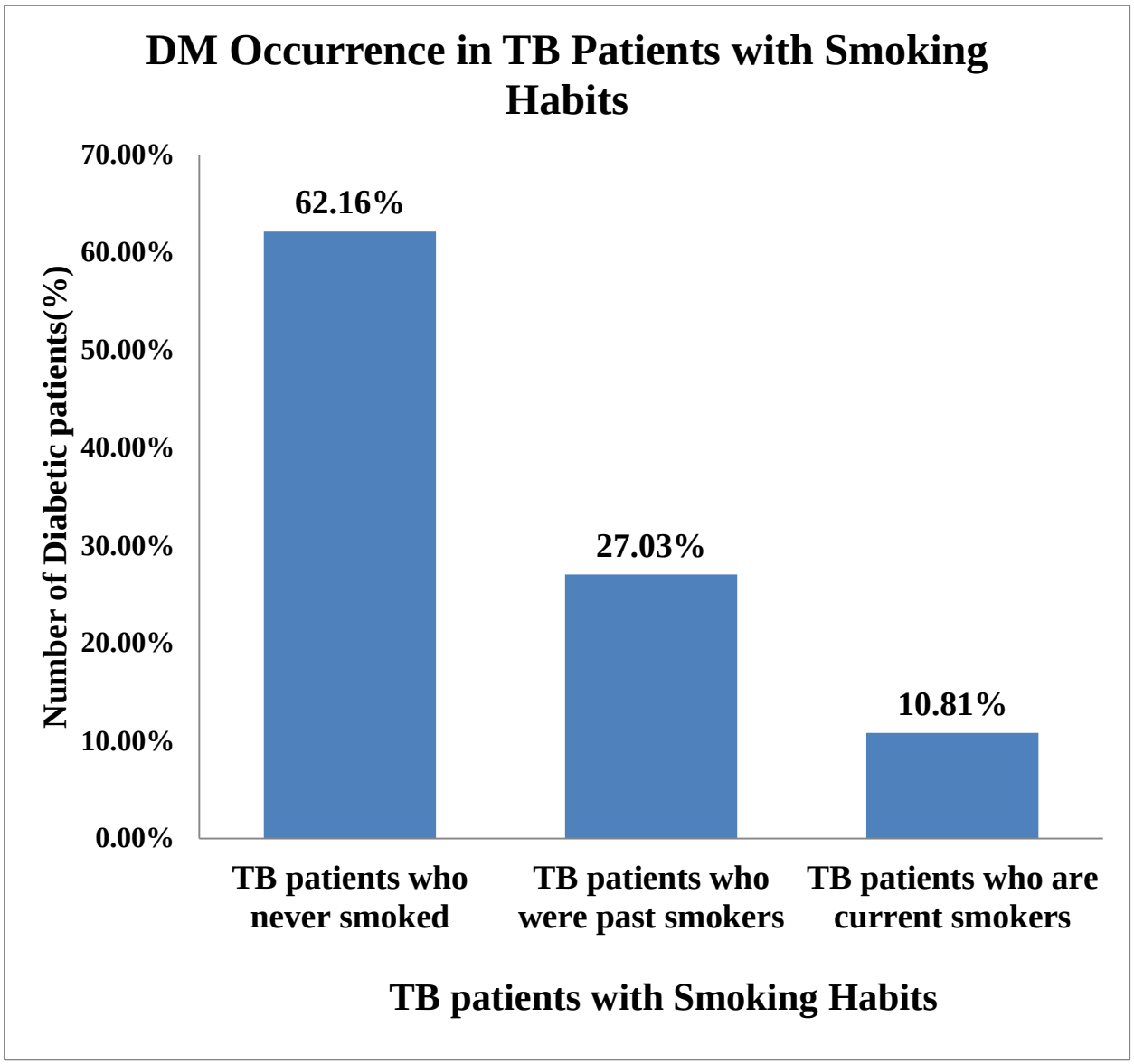

Figure 4.4.11: DM Occurrence in TB Patients with Smoking Habits

The sample of 100 patients showed that majority of TB patients having DM (62.16%) never smoked whereas minority of TB patients having DM (10.81%) were current smokers.

4.4.12 DM Occurrence in TB Patients habituated to Betel Leaves

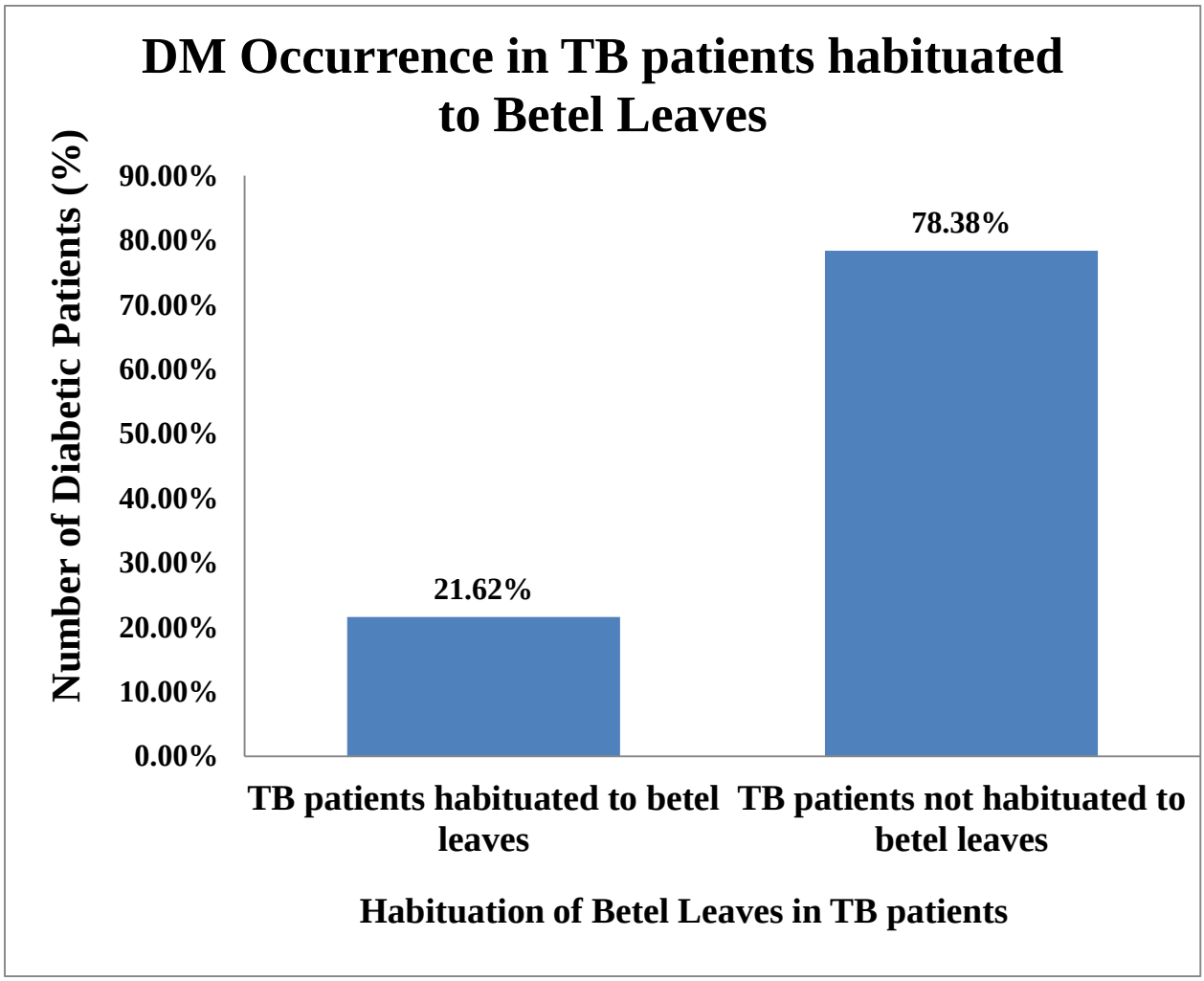

Figure 4.4.12: DM Occurrence in TB Patients habituated to Betel Leaves

The sample of 100 patients showed that majority of TB patients having DM (78.38%) were not habituated to betel leaves whereas minority of TB patients having DM (21.62%) were habituated to betel leaves.

CHAPTER FIVE
DISCUSSION & CONCLUSION

Discussion

In our study, 100 samples were analyzed, among them 61% were MDR-TB patients and 39% were TB patients. Previously published studies on TB focused either on the risk factors of TB or impact of DM on TB management without evaluating a clear cut correlation between DM & TB co infection in great detail. It is known from previous studies that diabetic patients are more prone to TB infection & reversibly TB infection can also have cumbersome effects on clinical outcome of diabetic patients. Here, we have studied the prevalence of diabetes in TB patients admitted to NIDCH hospital along with possible associated factors after going through the socio-demographic as well as clinical history of the TB patients.

In our study, among 100 TB patients, 37% patients were diabetic & 63% were non-diabetic. Among the diabetic patients, 10.80% had Type 1 DM & 89.20% patients had Type 2 diabetes. So, in our study we have found out that Type 2 diabetes had more association with TB. It is also noteworthy that Type 2 DM is the disease of the middle aged people and in our study we have found out that TB mainly occurs in middle aged people. So there may be a clear association between age and DM.

Among the diabetic TB patients, 45.94% patients were from 31-40 years, 16.23% were from 21-30 years, 21.62% were from 41-50 years, 13.51% were from 51-60 years age group. Around 75.68% patients had been suffering from diabetes for ≤5 years, 16.22% were for 6-9years & 8.10% were for ≥10 years. Their mostly suffered symptoms of hyperglycemia were increased thirst (32%), frequent urination (27%) & fatigue (26%) and weakness (59%).Almost 20% patients had the knowledge that diabetes can increase the chance of TB incidence & 80% patients did not have any idea. So this unawareness should be brought into account. Increase in health education will result in early diagnosis of both diabetes and TB, leading to better management of both coexisting together.

Among diabetic TB patients, 54.05% had no control in blood sugar level after diagnosis of DM with TB, 16.22% had controlled blood sugar level & 29.73% had no idea about this, as was self-reported. Incidence of DM & TB together can lead to problems in sugar control according to self-report of the patients.

Among diabetic patients, 37.84% had primary TB whereas 62.16% of them had MDR-TB.37.84% of TB patients and 62.16% of MDR-TB patients were diabetic, showing higher incidence of MDR-TB in diabetic patients. However, the sample of patients is too small to come to a definite conclusion. Among diabetic TB patients, 62.17% patients were male & 31.83% were female. So it is clearly indicated that male patients are more prone to having TB & DM together.

Majority of TB patients having DM (24.32%) were illiterate or from college whereas minority of TB patients having DM (13.52%) were from primary education. Here it is seen that mostly illiterate or those who have not got proper education have lack of knowledge for which they are more prone to DM & TB. So state of education can be an important issue which leads to more incidence of DM &TB together.

In this study, 37.84% of diabetic patients were previously diagnosed with TB once, 37.84% patients were diagnosed twice & 24.32% patients were diagnosed thrice. Here, 2.70% Diabetic TB patients had drinking habit, 8.11% had frequently drinking habit & 89.19% patients had no drinking habit. Again, 62.16% Diabetic TB patients never smoked, 27.03% were past smoker & 10.81% were current smoker. We cannot get any relationship of drinking & smoking habits with DM & TB. May be further studies can lead to better result regarding the relationship of smoking or drinking habits with TB & DM.

Jimenez-Corona *et al.* performed a study in Southern Mexico in TB patients & found 29.63% diabetes prevalence among 1262 patients. Jeon & Murray found the relative ratio of DM & TB approximately 3.11. They also noticed random effects of cohort studies which showed that DM was associated with an increased risk of TB. Goldhaber-Fiebert *et al.* found that increase in TB prevalence (4.7%) over time were more likely to occur when diabetes prevalence also increased. Viswanathan *et al.* performed a study in which out of 827 TB patients, 209 (25.3%) had diabetes. Jeon *et al.* performed a study which results in screening for TB in persons with DM, demonstrated that TB prevalence in this population is high, ranging from 1.7% to 36%. According to Baker *et al.* the global burden of DM is rising; the prevalence is estimated to reach 438 million by 2030 in TB patients. Our study shows the prevalence of DM in TB patients is 37%. This result shows some similarity with

the previous studies. But as our sample number is only 100, it is hard to come to a definite conclusion of prevalence of DM in TB patients. We are assuming that, most of the people of Bangladesh are ignorant of their health status and self-reported diagnosis is also very poor. So many people yet don't know whether they have diabetes or not. Probably we could get more diabetic patients if they were conscious or aware of their diseases.

Viswanathan *et al.* performed a study and showed that prevalence of diabetes was significantly higher in men compared to men 27.5% vs 20.2% women. In our study, 62.17% were male having DM & TB and 38.83% were female having DM & TB. This result is similar to previous result. So it can be said that male patients are prone to DM & TB incidence.

Amare *et al.* performed a study which shows the result that Pulmonary TB was occurring more often among patients with DM (>10 years). But here in our study, we have found only 8.10% patients were for ≥10 years. This variation may have come due to our small number of sample. So this issue requires further studies to be clarified.

There are several potential limitations to this study. Our analysis was based on estimates derived from observational studies that are vulnerable to confounding variables associated with both DM and TB. The data was collected according to patients' statement which was very subjective. Hence, there was a possibility of subjectivity and of selective under-reporting by patients or their relatives, which may have biased the results away from the true prevalence. Some symptoms of disease and duration of illness may have overlapped with other co-morbidities.

Conclusion

In summary, we found an increased risk of TB among people with diabetes despite heterogeneity in study design, underlying burden of TB, assessment of exposure and outcome, Data from these human studies are consistent with emerging information on the biological mechanisms by which hyperglycemia may affect the host susceptibility to TB. Our findings suggest that TB controls programs should consider targeting patients with diabetes for interventions such as active case finding and the treatment of latent TB and, conversely, those efforts to diagnose, detect, and treat DM may have a beneficial impaction TB control. We also recommend further studies investigating how TB risk varies by type, duration, and severity of DM, for a more thorough understanding of the association that could be translated to a clear public health message. Our another recommendation is to increase public awareness & serving them the knowledge about the risk factors or association of TB & DM together.

CHAPTER SIX
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QESTIONNAIRE

Name:	Date:

Sex: □ Male □ Female
Marital status: □ Single □ Married □ divorced

Age: □ <20 □ 21-30 □ 31-40 □ 41-50 □ 51-60 □ >60

Religion: □ Islam □ Hinduism □ Buddhism □ Christianity

Educational status:

□ Illiterate □ Primary □ Secondary □ College □ Graduate

□ Post-graduate

Occupation:

□ Govt. employee □ Private employee □ Private business □ Housewife

□ Student □ Garments worker □ Farmer

Income per month:

□ <5000 □5000-10,000 □10,000-25,000 □ >25,000

Weight: □30-40kg □40-50kg □ 50-60kg □ 60-70kg □ 0-10kg

Living with family: □ Yes □ No

Place of residence: □ Urban □ Rural □ Semi urban

How many people are living in the household?

□ 1-2 □3-4 □5-6 □7-8 □9-10 □11-12

How many people are living in the same room?

□ 1 □2 □3 □4 □5

Are you being diagnosed with TB for the first time? □Yes □No

If no, how many times were you diagnosed with TB? □1 □2 □3

Presence of TB patients in family currently: □Yes □No

Have your family members ever been diagnosed with TB? □Yes □No

If yes, then who? □Mother □Father □Wife/Husband □Brother

□Sister □Son/Daughter □ Other relatives

Plasma glucose (After 2hour): □50-100mg/dl □101-150mg/dl □151-200mg/dl □201-250mg/dl □251-300mg/dl □301-350mg/dl □351-400mg/dl

Creatinine: □0-0.5mg/dl □0.6-1mg/dl □1.1-1.5mg/dl □1.6-2.0mg/dl □2.1-2.5mg/dl □2.6-3.0mg/dl □3.1-3.5mg/dl

HbA1c: □0-5g/dl □6-10g/dl □11-15g/dl □16-20g/dl

Are you HIV-positive? □Yes □No

What is your smoking status? □Never a smoker □Past smoker □Current smoker

Do you drink alcohol? □Never □Infrequent/Frequent intermediate □Infrequent heavy □Frequent heavy

Do you have any kind of habituation of other toxic substances? □Yes □No □others

What symptoms do you suffer from?

□Cough □Haemoptysis □Fever □Shortness of breath □Chest pain □weakness

From which duration? □1-10days □11-20days □21-30days □31-40days □41-50days □51-60days □61-70days □71-80days □81-90days □91-100days □101-110days □111-120days □4-12months □1-2years

Time elapsed between onset of symptoms and duration:

□1-10days □11-20days □21-30days □31-40days □41-50days □51-60days □61-70days □71-80days □81-90days □91-100days □101-110days □111-120days □4-12months □1-2years

How was your TB diagnosed?

□Sputum for AFB □Chest X-ray □Historical Diagnosis (biopsy) □Clinical Diagnosis

What type of TB it is? □Pulmonary □Extra pulmonary □I don't know

Are you a MDR-TB patient? □Yes □No

In case of MDR-TB, have you completed your primary treatment? □Yes □No □I don't know

If not, then why? □Side effects □Unavailability of the medication □Lack of awareness □Reluctance on dot provider □Others

If MDR-TB patient, are you aware of the drugs you are resistance to?

□Yes □No

If yes, please mention : □Rifampicin □Isoniazid

What medications are you taking for TB? □Cat I □Cat II □Cat IV

What is/are the history of prior TB treatment?

□New TB regimen □Cat I relapse □Retreatment regimen

□Treated for MDR-TB □Cat II relapse

What is the cause of TB? □Infective organism □Heredity □Curse □Not aware □Smoking+alcohol+diet □Others

What is the mode of spread of TB? □Casual physical contact □Air □Not aware □Food utensils □Others

What do you know regarding diagnosis of TB?

□Long term □Don‘t know □Repeated occurrence □Infective □Air born □Diagnosed by cough

What do you know regarding treatment of TB?

□Long term □Don‘t know □Costly □Non treatable □Free govt. treatment □Lots of side effects □Curable

What do you know regarding prevention of TB?

□Non preventable □Don‘t know □Curable □Contagious

What sources of information do you have regarding TB?

□Health care workers □Mass media □Friends/Relatives who had TB □Other people in the community

Are you diabetic? □Yes □No □Don‘t know

If yes, what is the duration? □<5years □6-9years □>10years

What type of DM you have? □Type 1 □Type 2 □Don‘t know

If you have diabetes, what kind of medication are you on?

□Insulin □Metformin □Glicazide □Sitagliptin

Do you have a family history of diabetes? □Yes □No

Do you know what the symptoms of Hyperglycemia are? □Yes □No

Do you suffer from any of the symptoms of Hyperglycemia?

□Increased thirst □Frequent urination □Others □Fatigue □Weight loss □Blood sugar more than 180mg/dl □Headaches □Difficulty in concentrating □Blurred vision

If diabetic, how frequently do you meet the doctor? □Very often □Rarely □Twice in a year □Yearly □Whenever needed

If diabetic, how would you categorize your care for diabetes?

□Frequent care □Some care □None

For non diabetic patient, if you suspect diabetes, what will be your mode of action?

□Consult doctor □Take medicine

If you have diabetes, has your blood level been in control once you have been diagnosed with TB? □Yes □No □Don‘t know

Do you know that diabetes can increase chances of TB incidence?

□Yes □No

Put thick mark on the following side effects that you have suffered with:

Gastrointestinal Disorder:

□Nausea □Vomiting □Ulcers □Dyspepsia □Abdominal discomfort □Gastrointestinal bleeding □Diarrhea □Constipation

Ototoxicity:

□Tinnitus □Hearing loss □Deafness □Disequilibrium □Vertigo

Psychiatric Disorder:

□Irritability □Anxiety □Depression □Suicidal Ideation □Personality changes □Psychosis

Neurological Disorder:

□Dizziness □Insomnia □Parasthesia □Numbness □Seizures □Palpitation

Dermatological disorder:

□Skin reaction □Photosensitivity □Dry skin □Itching □Fungal infection □Skin reaction □Parasitic infection

Endocrine Disorder:

□Poor glycemic control □Hypothyroidism

Electrolyte Abnormalities:

□Dehydration □Hypocalcaemia □Hypomagnesaemia □Hypokalaemia □Renal insufficiency □Protein deficiency

Arthralgia:

□Joint pain □Ankle swelling and pains □Arthritis

Others:

□Weight loss □ anemia □ Body weakness □ Fever □ Hair loss □ Heart failure □ Hypertension □ Heart burn □ Loss of appetite □ Vitamin deficiency □ Urinary tract infection □ Shortness of breath □ Asthma □ Tachycardia □ Hypotension

Mention the name of other drugs if are taking for other diseases.

□Omeprazol □Domperidon □BlC □Mebendazole □Pyridoxine Hydrochloride □Diazepam/Chlorazepam □Diclofenac □Clostridium □ Saline □Calcium Supplement □Paracetamol □Amoxicillin □Tiemonium methylsulphate □Amino acid supplement □Oxygen inhalation/ Nebulizer □Blood Supply □Thyroxin □Rupatidine □Procyclidine hydrochloride □ Febuxostat □Riboflavin □Metronidazole □Glucocorticoid