"Prevalence and determinants of depression in diabetic patients: An observational study in a tertiary care center in Ahmedabad region"

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CLINICAL PHARMACY

BY

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CERTIFICATE

This is to certify that the dissertation work entitled "Prevalence of depression in diabetic patients: A cross – sectional study in tertiary care center in Ahmedabad region" submitted by Ms. Kavisha Raval with Regn. No. (16MPH704) in partial fulfillment for the award of Master of Pharmacy in "Clinical Pharmacy" is a bonafide research work carried out by the candidate at the Department of Pharmacology, Institute of Pharmacy, Nirma University under our guidance. This work is original and has not been submitted in part or full for any other degree or diploma to this or any other university or institution.

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DECLARATION

I hereby declare that dissertation entitled *"Prevalence and determinants of depression in diabetic patients: An observational study in a tertiary care center in Ahmedabad region"* is based on the original work carried out by me under the guidance of Dr. Snehal S. Patel, Assistant professor, Department of Pharmacology, Institute of Pharmacy, Nirma University. I also affirm that this work is original and has not been submitted in part or full for any degree or diploma to this or any other university or institution.

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I – LIST OF ABBREVIATIONS

DM	Diabetes Mellitus
IDF	International Diabetes Federation
CAD	Coronary Artery Disease
PHQ-9	Patient Health Questionnaire- 9
GDM	Gestational Diabetes Mellitus
IDDM	Insulin Dependent Diabetes Mellitus
NIDDM	Non-insulin Dependent Diabetes Mellitus
ADA	American Diabetes Assoiation
T1DM	Type-1 Diabetes Mellitus
HLA	Human Leukocyte Antigen
HPA-axis	Hypothalamic pituitary adrenal axis
GLUT	Glucose transporters
cAMP	Cyclic adenosine monophosphate
IGF	Insulin-Like Growth Factor
NICE	National Institute for Clinical Excellence
T2DM	Type-2 Diabetes Mellitus
MCP-1	Monocyte chemo tactic protein-1
BMI	Body Mass Index
SSRI	Selective serotonin reuptake inhibitors
TCA	Tricyclic antidepressants

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Chapter 1

Abstract

Background:

Diabetes mellitus doubles the chances of suffering from depression. Depression and diabetes shared the bidirectional association. Co-occurrence of diabetes and depression has been established in clinical studies, which is associated with increased impairment as well as mortality. It is crucial to know the prevalence of depression in diabetes and its association with various risk factors.

The objective of the study:

The objective of present study was to determine the prevalence of depression and to determine associated risk factors among diabetes patients in Ahmedabad region.

Methodology:

An observational, single-centric and prospective study was performed in Dia-care: Diabetes care and hormone clinic, Ahmedabad. Total 360 diabetic patients were included in this study to diagnose depression. The clinical interview was carried out using (Patient Health Questionnaire) PHQ-9 questionnaire. To access associated risk factors, socio-demographic characteristics of the patient, physical activity, marital status, family history, duration of diabetes, HbA1c level, systolic and diastolic blood pressure and diabetic complications were evaluated.

Results:

64.72% patients (N= 233) were found to be suffering from depression among them 55.56% were mildly depressed, 7.78 % were moderately depressed, and 1.39 % were suffering from severe depression. Significant association was found between diabetes-associated depression and duration of diabetes ($P < 0.0001$), quality of sleep ($P < 0.0001$), education ($P < 0.0001$), occupation ($P < 0.0001$), hypertension ($P < 0.0001$), dyslipidemia ($P < 0.0001$), Body Mass Index ($P – 0.0002$), diabetic complications ($P < 0.0001$), marital

status (P – 0.0471), age (P < 0.0001), gender (P – 0.0213) and physical activity (P <0.0001). There was no significant association found between diabetes-associated depression and type of diabetes, HbA1c range and family history.

Conclusion:

The present study conclude that diabetic patients need detailed psychiatric analysis to rule out depression, which further complicates the treatment of the patient.

Chapter 2

Introduction

Diabetes impacts on more than 360 million people worldwide, and it may increase to 552 million by 2030 (Whiting et al., 2011). India will be the second highest diabetic population of 69.9 million by 2025. Diabetes continues rises due to rapid cultural changes and social changes in aging population, urbanization, change in diet habits and sedentary lifestyle. The prevalence varies from 5% to 17%, with higher level found in southern parts of India.

People with diabetes also have a negative impact on psychological well being. They often experience stigma, and it leads to fear and disgust from others. These further leads to feeling discriminated; poor psychological well-being and it will affect their self-care (Schabert et al. 2013). People with diabetes frequently feel negative experiences when it comes to the injecting insulin in public places. One study suggested that people with diabetes relate their negative experience with the general public's unawareness about diabetes and its management. As a result, the people with diabetes realize that general public is mistaking them as a drug addict or holding the belief that diabetes is developed by eating excessive food (Tak-Ying et al. 2003).

The projection of diabetes depends upon the patient's adherence to the self-management regime. Psychological factors can be the reason behind Lack of self-management, which includes not accepting the diagnosis, depression and believe that self-management is very difficult (Naude et al., 2007).

A chronic condition like diabetes can affect various organs and systems in the body includes nephropathy, retinopathy, neuropathy, cardiovascular disease including heart disease and stroke (Shaw & Cummings et al., 2012). Patients who have poor self-management to control diabetes and diagnosis of diabetic complications often feel intense guilt (Harris et al., 2003).

Diabetic patients in India have one of the lowest levels of psychological well - being based on WHO (World Health Organization) well – being index, with 41% reported as a poor psychological well – being, especially among lower income group. Diabetes is also

associated with anxiety (Li et al., 2008; Penckofer, Ferrans, Velsor - Friedrich, & Savoy, 2007), feelings of anger (Penckofer et al., 2007) and depression (Egede & Ellis et al., 2010). Depression is a public health concern regarding its prevalence, economic burden, morbidity, and suffering. The estimated prevalence of depression is 25% worldwide. Depressive disorders are seen more in women than men. In the total lifespan of a human, there are 10-20% chances of suffering from depression. Some research has demonstrated that depression has a negative impact on the quality of life of people with diabetes and it is related to poor glycemic control, worsen the cardiovascular complication and increased health care services.

The International Diabetes Federation has also stressed the importance of integrating psychological care in the management of diabetes. A meta-analysis shows the comparison between the people with diabetes and people without diabetes, people with diabetes have 24% more risk of developing depression (Nauwen et al., 2010). Comparison between the people with diabetes and low level of depression and people with diabetes and moderate to high level of depression are less likely to adhere to oral medication and diet recommendation (Ciechanowski, Katon, & Russo, 2000). Ciechanowski, Katon, Russo, & Hirsch (2003) suggest that due to an association between the symptom reporting of diabetes and adherence to the self-management it is required to identify the symptoms of depression in people with diabetes. Some of the symptoms related to depression like weight gain, overeating, and losing interest in self-care can, can worsen diabetes.

Depression has been found, and it can be related to poor glycemic control, which is one of the significant factors leads to diabetic complications (Lustman et al., 2000). Depression is commonly seen in the patients with diabetic complications (de Groot, Anderson, Freedland, Clouse, & Lustman, 2001; Pouwer et al., 2003) and increased levels of diabetes-related stress (Pouwer et al., 2003). One study suggested that type-2 diabetes people who reported with the high level of depression had a negative impact on insulin

therapy. This includes the feeling of failure and struggling to manage insulin injections (Makine et al., 2009).

Depression and diabetes share a bidirectional causal association. Depression has been postulated to play a causal role in the emergence of diabetes (Balhara et al. 2011). Co-occurrence of diabetes and depression has been established in clinical as well as general population studies (Katon et al.). Dysregulation of the hypothalamic pituitary adrenal axis in the brain is known to occur in both depression and diabetes. A natural biological response to stress is for the body to increase cortisol levels. Prolonged periods of stress may result in chronic hyperactivity of the axis that is positively associated with both visceral adipose (fat) and insulin resistance. Subclinical hypercortisolism is one potential physiological link between depression and diabetes (Champaneri et al. 2010).

Difficulties sleeping, either too much or too little, are classic symptoms of depression and increase the risk of suicide (Nutt et al.2008). Sleep apnea is a known risk factor for the development of diabetes (Wang et al. 2013). Altered circadian rhythms, especially little sleeping, have been shown to impair glucose regulation, increase insulin resistance, and the risk of diabetes onset (Mallon et al. 2005) (Yaggi et al. 2006). Disruption of quality sleep patterns provides another potential physical link between these two chronic conditions (Holt et al. 2014) (Snoek et al. 2015).

Alteration in the glucose transport systems has been hypothesized as links between depression and diabetes. Although no causal pathway has been identified, it is possible that abnormalities in glucose handling and storage could lead to depression in diabetes. General dysregulation of physiological systems and neuroendocrine alterations of the hypothalamic pituitary adrenal axis, autonomic nervous system, immune system, glucose transport systems or circadian rhythms could manifest themselves as both symptoms of depression and diabetes (Lett et al. 2004) (Musselman et al. 2003).

Depression can directly inhibit a patient with diabetes' ability to be engaged efficiently even in the best-prepared, proactive treatment program. They may have diminished compliance with taking their prescribed diabetes or depression medications, checking their blood sugar levels, attending the medical appointments or participating in their recommended diet and exercise regimes.

The prevalence was seen 35 % in South India (Sendhilkumar et al. 2017) and 38.75% in North Indian community (Mushtaque et al. 2016; Singer et al. 2009). Data on this association is mostly from western countries, and few researchers from India have worked in this direction. More data is available from South India, and there has been a shortage of work on West India population. Therefore, the purpose of present study was to address the following need, 1) to increase the knowledge of prevalence of diabetes associated depression and 2) To strengthen the understanding of the correlation of socio-emotional and socio-environmental factors with resultant suffering. This will further help patients to resolve challenges in self-management. Better self-management can be turned into the improved health status and fewer complications.

Chapter 3

Review of Literature

3.1 Introduction of Diabetes Mellitus:

Diabetes mellitus is known as a collection of disorders that have glucose intolerance and hyperglycemic condition as their hallmark, either due to impaired insulin action or insulin deficiency, or combination of both. To understand diabetes it is required to understand normal physiological process, which occurs during and after a meal. Food passes through the gastrointestinal tract, whereas carbohydrates, fat, proteins along with nutrients absorbed into the blood. The Carbohydrate signals pancreas, to secrete insulin in presence of sugar. Insulin increases the uptake and storage of sugar by all tissues in the body, mainly the liver, musculature and fat tissues (Roussel et al. 1998).

Permanent cure for diabetes is yet to be discovered but it can be controlled by maintaining blood sugar levels through diet, exercise and medication and reduce the risk of long-term diabetes complications. Long-term complications include:

- Cardiovascular system – Thickening of arteries, heart disease and stroke (Heart Foundation, 2003)
- Kidney – Kidney failure, kidney disease and Nephropathy
- Nerves – Neuropathy (Gradually damaging the nerves)
- Feet – Diabetic foot, ulcers, infections etc.
- Eyes – Cataract and retinopathy (Gradually damaging the eyes)

This progressive natured disease required constant glycemic control and proper therapeutic regimens. When single agent is not achieving glucose level, there is a need to add second and third agent to control blood glucose level more effectively.

Classification of Diabetes Mellitus:

According to the World Health Organization, Diabetes is a metabolic disorder characterized by hyperglycemia with disturbance in carbohydrate, fat and protein metabolism.

Diabetes mellitus is mainly classified into categories like Type 1 diabetes, Type 2 diabetes and gestational diabetes.

I. Insulin Dependent Diabetes Mellitus (T1DM)

The subclass of diabetes, type I diabetes, is generally characterized by the abrupt onset of severe symptoms, dependence on exogenous insulin to sustain life and proneness to ketosis even in the basal state, all of which is caused by absolute insulin deficiency. IDDM is the most prevalent type of diabetes among children and young adults in developing countries, and was formally termed juvenile diabetes (Harris and Zimmet, 1997). It is a catabolic disorder in which circulating insulin is virtually absent, plasma glucagon is elevated, and the pancreatic B cells fail to respond to all insulinogenic stimuli (Nolte and Karam, 2001).

Type I diabetes is thought to result from an infectious or toxic environmental contingency in people whose immune systems are genetically predisposed to develop a vigorous autoimmune response against pancreatic B cell antigens. Extrinsic factors that might affect B cell functioning include damage caused by viruses such as the mumps virus and coxsackie virus B4, by chemical agents, or by destructive cytotoxins and antibodies released from sensitized immunocytes. An underlying genetic defect relating to pancreatic B cell replication or function may predispose a person to the development of B cell failure after viral infections. In addition, specific HLA genes may increase susceptibility to a diabetogenic virus or may be linked to certain immune response genes that predispose patients to a destructive autoimmune response against their own islet cells (auto-aggression). Observations that pancreatic B cell damage appears to be lessened when immunosuppressive drugs such as cyclosporine or azathioprine are given at the initial manifestation of type I diabetes support the importance of auto-aggression by the immune system as a major factor in the pathogenesis of this type of diabetes (Nolte and Karam, 2001).

II. Non-insulin Dependent Diabetes Mellitus (T2DM)

Type II diabetes greatly out numbers all other forms of diabetes. Patients with NIDDM are not dependent on exogenous insulin for prevention of ketonuria and are not prone to ketosis. However, they may require insulin for the correction of fasting hyperglycemia if this cannot be achieved with the use of diet or oral agents, and they may develop ketosis under special circumstances such as severe stress precipitated by infections or trauma (Harris and Zimmet, 1997).

The pathogenesis in type II diabetes is that the pancreas produces insulin but the body does not utilize the insulin correctly. This is primarily due to peripheral tissue insulin resistance where insulin-receptors or other intermediates in the insulin signaling pathways within body cells are insensitive to insulin and consequently glucose does not readily enter the tissue leading to hyperglycemia or elevated blood glucose concentrations (Albright, 1997). Obesity, which generally results in impaired insulin action, is a common risk factor for this type of diabetes, and most patients with type II diabetes are obese (Nolte and Karan, 2001) and will ultimately require multiple anti-diabetic agents to maintain adequate glycaemic control (Gerich, 2001).

III. Gestational diabetes

Gestational diabetes mellitus (GDM) resembles T2DM in several respects and involves a combination of moderately inadequate insulin secretion and sensitivity. It occurs in about 2–5% of all pregnancies and may progress or disappear after delivery. Gestational diabetes is completely treatable but requires careful medical supervision throughout the pregnancy. About 20–50% of affected women develop T2DM later on in life.

Epidemiology of Diabetes:

Pathophysiology of Diabetes:

The endocrine Pancreas:

The human pancreas is basically composed of two types of secretory cells that are both involved in nutrient handling: 98% of the cells- the exocrine type – secrete a food-processing enzyme-bicarbonate mixture into the duodenum, while the remaining 2% - the endocrine type- have a metabolic function and secrete a mixture of nutrient-generated hormones into the portal vein. This small endocrine part is of vital importance in maintaining glucose homeostasis through the action of the 51-amino acid peptide insulin. Four endocrine cell types can be distinguished: A cells (alpha), B cells (beta), D cells (delta) and PP cells (pancreatic polypeptide) (Klöppel and In't Veld, 1997). These endocrine cells are distributed throughout the pancreas in areas known as islets.

Diabetes-related islet changes

The islet changes, from a morphological point of view, associated with various types of diabetes can be divided into those with and without severe beta-cell loss. Severe beta-cell loss is found in type I diabetes and some uncommon forms of diabetes such as virus-related diabetes and congenital diabetes. Islets without severe loss of beta cells are encountered in type II diabetes and in the secondary forms of diabetes (Klöppel and In't Veld, 1997).

Insulin:

The beta cells of the pancreatic islets synthesize insulin from a single chain precursor of 110 amino acids termed preproinsulin. After translocation through the membrane of the rough endoplasmic reticulum, the 24-amino-acid N-terminal signal peptide of preproinsulin is rapidly cleaved off to form proinsulin. Here the molecule folds and the disulfide bonds are formed. On the conversion of human proinsulin to insulin in the Golgi complex, four basic amino acids and the remaining connector or C peptide are removed by proteolysis. This gives rise to the two-peptide chains (A and B) of the insulin molecule, which contains one intra-subunit and two inter-subunit disulfide bonds. The A chain usually is composed of 21 amino acids and the B chain 30. The two chains of insulin form

a highly ordered structure with several helical regions in both the A and B chains (Figure 3.1).

Two ions of Zn2+ are coordinated in a proinsulin hexamer and this form of insulin presumably is stored in the granules of the pancreatic ß cells. It is believed that Zn2+ has a functional role in the formation of crystals and that crystallization facilitates the conversion of proinsulin to insulin, as well as the storage of the hormone (Davis and Granner, 1996).

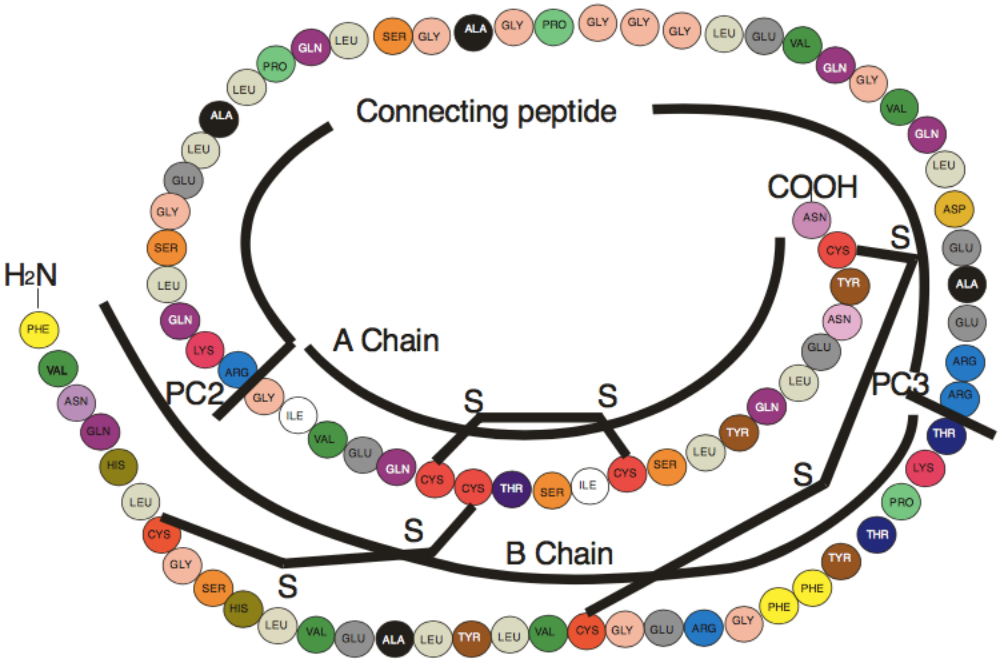


Figure 3.1. Structure of human proinsulin. Insulin is shown as the shaded peptide chains, A and B (Davis and Granner, 1996).

Insulin secretion

Insulin is released from pancreatic ß-cells at a low basal rate and at a much higher rate in response to a variety of stimuli, especially glucose. Hyper glycaemia results in increased

intracellular A TP (adenosine triphosphate) levels, which close the A TP-dependent potassium channels. Decreased outward potassium current through this channel results in depolarization of the ß-cell and the opening of voltage-gated calcium channels. The resulting increased intracellular calcium triggers the secretion of the hormone (Figure 3.2).

Insulin degradation

The liver and kidney are the two main organs that remove insulin from circulation, presumably by hydrolysis of the disulfide connection between the A and B chains through the action of glutathione insulin transhydrogenase (insulinase). After this reductive cleavage further degradation by proteolysis occurs. The liver normally clears the blood of approximately 60% of the insulin released from the pancreas by virtue of its location as the terminal site of the portal vein blood flow, with the kidneys removing 35 – 40% of the endogenous hormone. However, in insulin-treated diabetics receiving subcutaneous insulin injections, this ratio is reversed, with 60% of exogenous insulin being cleared by the kidney and the liver removing no more than 30-40%. The half-life of circulating insulin is 3-5 minutes (Nolte and Karam, 2001).

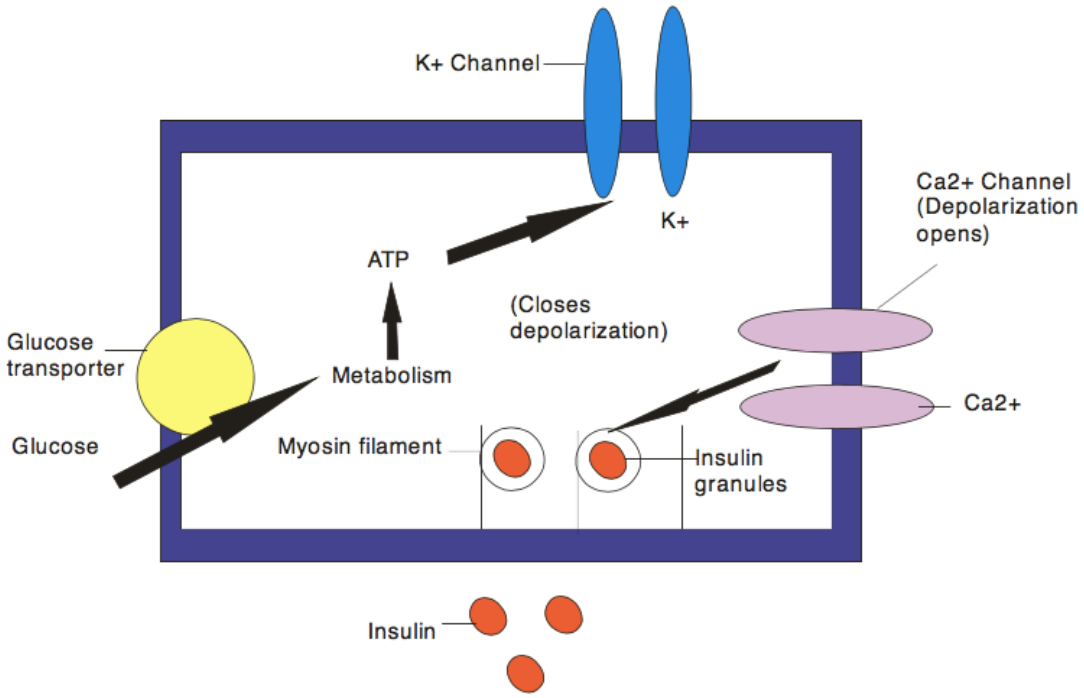


Figure 3.2. Model of the control of insulin release from the pancreatic ß-cells by glucose (Nolte and Karam, 2001).

The insulin receptor

Once insulin has entered the circulation, it is bound by specialized receptors that are found on the membranes of most cells. However, the biological responses promoted by these insulin–receptor complexes have only been identified in a few target tissues, e.g. liver, muscle and adipose tissue. The receptors bind insulin with high specificity and affinity in the picomolar range. The full insulin receptor consists of two heterodimers, each containing an alpha subunit, which is entirely extra cellular and constitutes the recognition site, and a beta subunit that spans the membrane (Figure 3.3). The ß- subunit contains a tyrosine kinase. When insulin binds to the alpha subunit on the outer surface of the cell, tyrosine kinase activity is stimulated in the beta portion. Although the ab dimeric form is capable of binding insulin, it does so with a much lower affinity than the tetrameric aabb

form. Self– phosphorylation of the ß portion of the receptor causes both increased aggregation of aß heterodimers and stabilization of the activated state of the receptor tyrosine kinase.

In clinical situations associated with elevated levels of circulating insulin, such as obesity or insulinoma, the concentration of insulin receptors is reduced. This down regulation of insulin receptors seems to provide an intrinsic mechanism whereby the target cells limit their response to excessive hormone concentrations (Nolte and Karam, 2001).

Effects of insulin on its targets

Insulin promotes the storage of fat as well as glucose within specialized target cells and influences cell growth and the metabolic functions of a wide variety of tissues.

Action of insulin on glucose transporters (GLUT)

Insulin has an important effect on several transport molecules that facilitate glucose movement across cell membranes. These transporters may play a role in the etiology as well as the manifestation of diabetes. GLUT 4, quantitatively the most important in terms of lowering blood glucose, is inserted into the membranes of muscle and adipose cells from intracellular storage vesicles by insulin. Defects in GLUT 2 mediated transport of glucose into pancreatic ß-cells may contribute to the reduced insulin secretion that characterizes type II diabetes.

Action of insulin on the liver

The first major organ reached by endogenous insulin via the portal circulation is the liver, where its function is to increase storage of glucose as glycogen and to reset the liver to the fed state by reversing a number of catabolic mechanisms, such as glycogenolysis,

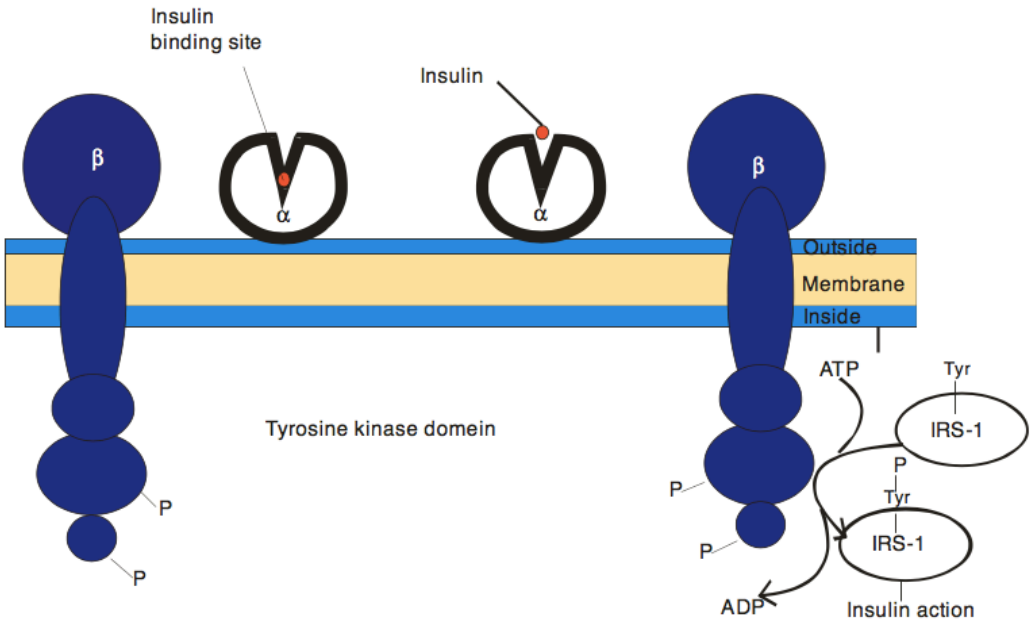


Figure 3.3. Schematic diagram of the probable structure of the insulin receptor tetramer in the activated state (Nolte and Karam, 2001).

Ketogenesis, and gluconeogenesis, which are associated with the post-absorptive state. These effects are brought about directly through insulin-induced phosphorylations, which activate pyruvate kinase, phosphofructokinase and glucokinase, while reprieving gluconeogenic enzymes, including pyruvate carboxylase, phosphoenolpyruvate carboxykinase, fructose bisphosphatase, and glucose 6-phosphatase. Insulin also exerts indirect effects to decrease hepatic gluconeogenesis and ketogenesis by reducing the fatty acid flux to the liver through its antilipolytic action on adipocytes. In addition, insulin decreases urea production, protein catabolism, cAMP (cyclic adenosine monophosphate) in the liver, promotes triglyceride synthesis and, increases potassium and phosphate uptake by the liver.

Effect of insulin on muscle

Insulin promotes protein synthesis by increasing the amino acid transport and by stimulating ribosomal activity. It also promotes glycogen synthesis to replace the glycogen stores expended by muscle activity. Increasing the glucose transport into the muscle cells, inducing glycogen synthase, and inhibiting glycogen phosphorylase accomplish this.

Effect of insulin on adipose tissue

Insulin acts on reducing circulating free fatty acids and promoting triglyceride storage in adipocytes by three mechanisms:

1) Induction of lipoprotein lipase, which actively hydrolyzes triglycerides from circulating lipoproteins;
2) Glucose transport into cells to generate glycerophosphate as a metabolic product, which permits esterification of fatty acids supplied by lipoprotein hydrolysis; and
3) Reduction of intracellular lipolysis of stored triglyceride by a direct inhibition of intracellular lipase (Nolte and Karam, 2001).

Diagnosis of diabetes:

The clinical diagnosis of diabetes is often prompted by symptoms such as increased thirst and urine volume, recurrent infections, unexplained weight loss and in severe cases, drowsiness and coma; high levels of glycosuria are usually present. Single blood glucose can establish the diagnosis in diabetes.45

The World Health Organization classified the diagnostic criteria for both type 1 and type 2 as given below:

Table 3.5.1: Diagnostic criteria for diabetes

Condition	Fasting Blood glucose	Postprandial blood glucose	HbA_{1c} (%)
Normal	<6.1mmol/l (<110 mg/dl)	<7.8mmol/l (<140mg/dl)	<6.0
Impaired fasting glucose (IFG)	≥ 6.1to 6.9 mmol/l (110 to 126mg/dl)	<7.8 (<140mg/dl)	6.0–6.4
Impaired glucose tolerance (IGT)	<7.0 mmol/l(<126mg/dl)	≥7.8 (≥140mg/dl)	6.0–6.4
Diabetes mellitus	≥7.0mmol/l (≥126 mg/dl)	≥11.1 (≥200mg/dl)	≥6.5

Diabetes Risk Factors:

Risk Factor	Nature of the Association
Age	Risk increases with age and is more common in seniors than younger adults
Sex	More men than women develop diabetes
Race/ethnicity/culture	Descendants of Aboriginal, African, Asian, Hispanic or South Asian populations are at increased risk of diabetes
Socioeconomic status (SES)	Low SES adults are at increased risk of diabetes
Physical inactivity	Adults with sedentary lifestyles are at risk of diabetes
First-degree relative	Having at least one first-degree relative with type 2 diabetes increase the risk of diabetes
Prediabetes	A history of impaired glucose tolerance (IGT), impaired fasting glucose (IFG), or HbA1C 6.0%–6.4% increases the risk of diabetes
Gestational diabetes	A history of gestational diabetes increases the risk of type 2 diabetes
Macrosomic infant	A history of delivering a macrosomic infant (≥ 4.5 kg) increases the risk of diabetes
End organ damage	The presence of end organ damage complications is associated with diabetes: • Microvascular (retinopathy, neuropathy, nephropathy) or • Macrovascular (coronary, cerebrovascular, peripheral)
Vascular risk factors	The presence of the following vascular risk factors increases the risk of diabetes: • HDL cholesterol <1.0 mmol/L in males, <1.3 mmol/L in females • Triglycerides ≥1.7 mmol/L • Hypertension • Overweight (BMI ≥ 25 kg/m2) • Abdominal obesity
Associated diseases/conditions	The presence of the following associated conditions increases the risk of diabetes: • Polycystic ovary syndrome • Acanthosis nigricans • Obstructive sleep apnea • Psychiatric disorders (bipolar disorder, depression, schizophrenia) • Human immunodeficiency virus (HIV) infection and highly active antiretroviral therapy
Drugs associated with diabetes	The use of the drugs such as glucocorticoids or atypical antipsychotics increases the risk of diabetes

Adapted From: (Canadian Diabet**es Association, 2013)**

Complications of Insulin Therapy:

Oral hypoglycemic agents/insulin is the mainstay of the treatment of diabetes and is effective in controlling hyperglycemia. However, it has prominent side effects and fails to significantly alter the course of diabetic complications (Rang and Dale, 1991). The main complications of insulin therapy are 1) Hypoglycemia which may result from a delay in taking a meal, unusual physical exertion or a dose of insulin that is too large for immediate needs. Autonomic warning signals of hypoglycemia and the manifestation of insulin excess are mainly those of impaired functions of the central nervous system such as mental confusion, bizarre behavior and ultimately coma. More rapid development of hypoglycemia from the effects of regular insulin use causes signs of autonomic hyperactivity; both sympathetic (tachycardia, palpitations, sweating, tremulousness) and parasympathetic (nausea, hunger) that may progress to convulsions and coma if untreated. 2) Immunopathology of insulin therapy includes i) insulin allergy, ii) immune insulin resistance (development of anti-insulin antibodies) and iii) lipodystrophy at injection sites (Nolte and Karam, 2001).

Oral Anti diabetic Agents:

Four categories of oral ant diabetic agents are available namely; insulin secretagogues, biguanides, thiazolidinedione, and alpha-glycosidase inhibitors (Nolte and Karam, 2001).

Insulin secretagogues: sulfonylureas

The major action of sulfonylureas is to increase insulin release from the pancreas. Sulfonylureas binds to a 140kDa high-affinity sulfonylurea receptor that is associated with a beta cell inward rectifier-type ATP-sensitive potassium channel. The binding of a sulfonylurea inhibits the efflux of potassium ions through the channel and results in depolarization. Depolarization, in turn, opens a voltage-gated calcium channel that results in a calcium influx and the release of insulin. Insulin synthesis is not stimulated and may even be reduced by sulfonylureas. Some evidence indicates that after prolonged

sulfonylurea therapy, serum insulin levels no longer increase but may even decrease. It was also established that chronic administration of sulfonylureas to type 2 diabetic patients reduced serum glucagon levels but increased the binding of insulin to the tissue receptors (Nolte and Karam, 2001). Seven sulfonylurea drugs are available in the USA and are conventionally divided into first and second-generation agents, which differ primarily in their potency. The first-generation includes tolbutamide, tolazamide, acetohexamide and chlorpropamide and the second generation includes glyburide, glipizide and glimepiride.

Insulin secretagogues: meglitinides

Meglitinides are a new class of insulin secretagogues. Repaglinide, the first member of the group, was approved for clinical use by the FDA in 1998. These drugs modulate Beta cell insulin release by regulating potassium efflux through the potassium channels. Meglitinides and sulfonylureas overlap in their molecular binding sites since meglitinides have two binding sites in common with sulfonylureas and one unique binding site. They have however, no direct effect on insulin exocytosis as does sulfonylureas (Nolte and Karam, 2001).

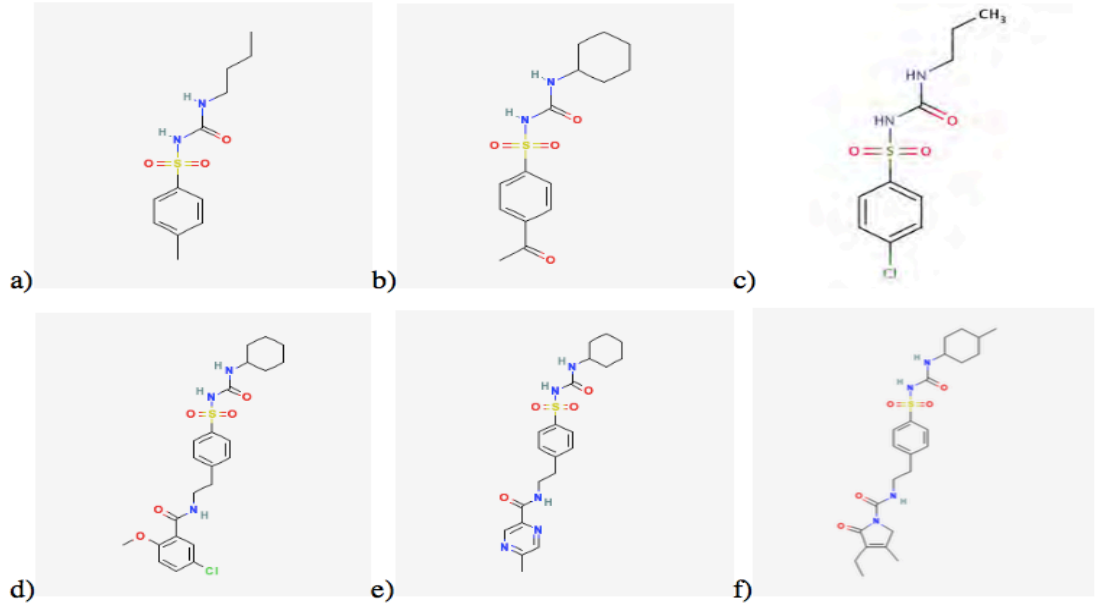


Figure 3.4 Chemical structure of the first generation sulfonylurea (a) tolbutamide, (b) tolazamide (c) chloroproamide and the second generation sulfonylurea (d) glyburide (e) glipzide and (f) glimepiride (PubChem Public Chemical Database, 2009).

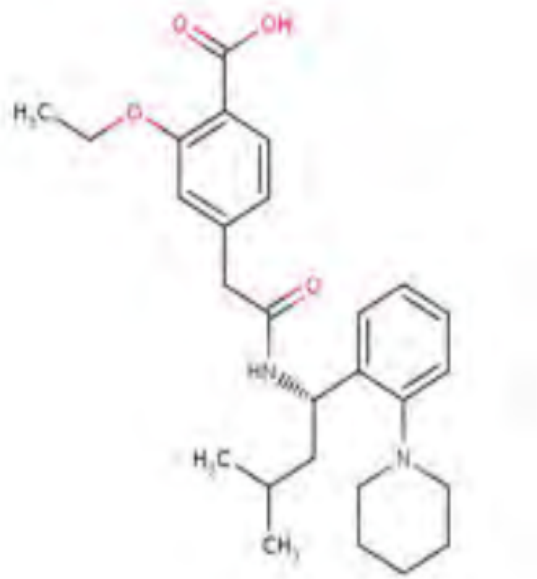


Figure 3.5 Chemical structure of the meglitinide repaglinide (PubChem Public Chemical Database, 2009).

Biguanides

Three types of biguanides are being used in the treatment of diabetes namely phenformin, buformin and metformin. The use of the first two mentioned was discontinued in the United States of America due to its association with lactic acidosis (Nolte and Karam, 2001).

Metformin originates from the French lilac, Galega officinalis L., a perennial herb known for centuries to reduce the symptoms of diabetes. The active compound is galegine, a guanidine derivative. Metformin's clinical trails were successfully completed in 1995 and its use approved in the United States of America. The full extent of the mechanism of the

action of biguanides is unknown, but its blood glucose-lowering action does not depend on the presence of functioning pancreatic beta cells. Proposed mechanisms of action includes direct stimulation of glycolysis in the tissue, and the increase of glucose removal from the blood; reduced hepatic gluconeogenesis; slowing of glucose absorption from the gastrointestinal tract; with increase glucose to lactate conversion by enterocytes and the reduction of plasmaglucagon levels (Nolte and Karam, 2001).

Biguanides have been most often prescribed for patients with refractory obesity whose hyperglycemia is due to insulin resistance. As metformin is an insulin-sparing agent and does not increase weight or provoke hypoglycemiait it has the advantage over insulin and sulfonylureas in treating hyperglycemia. The most frequent toxic affects of metformin are gastrointestinal and there is a risk of lactic acidosis.

Thiazolidinediones

Thiazolidinediones is a recently introduced class of oral antidiabetic drug that enhances target tissue insulin sensitivity. Two types are commercially available namely rosiglitazone and pioglitazone. The exact mechanism of their action is not known, but their major action is to diminish insulin resistance in muscle and adipose tissue.

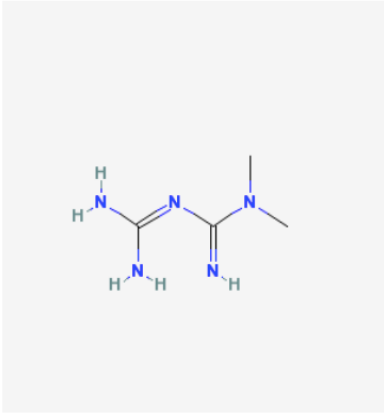


Figure 3.6 Chemical structure of the biguanide metformin (PubChem Public Chemical Database, 2009).

Troglitazone was the first thiazolidinedione to be approved but was withdrawn due to its association with a low but significant rate of idiosyncratic liver damage. Two other thiazolidinediones namely rosiglitazone and pioglitazone demonstrated efficacy similar to that of troglitazone but with no evidence of hepatictoxoxicity (Nolte and Karam, 2001).

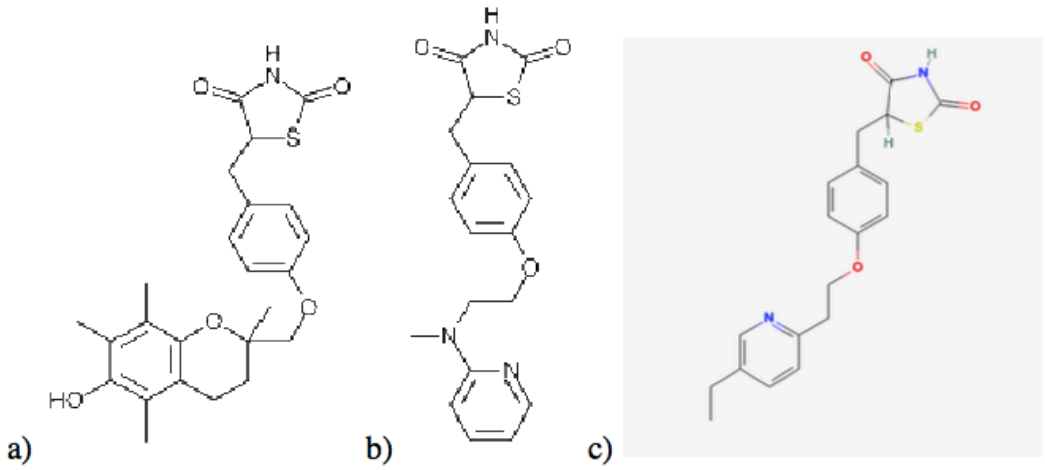


Figure 3.7 Chemical structure of the thiazolidinediones, a) troglitazone, b) rosiglitazone and c) pioglitazone (PubChem Public Chemical Database, 2009)

Alpha-glucosidase inhibitors

Acarbose and miglitol are the two agents available in this class. Alpha-glucosidase inhibitors act by inhibiting the enzymes, pancreatic alpha-amylase and alpha-glucosidase, found in the brush border cells that line the small intestine. They cleave the more complex carbohydrates such as starches, oligosaccharides and disaccharides into monosaccharide molecules before being absorbed in the duodenum and upper jejunum (Luna and Feinglos, 2001; Nolte and Karam, 2001). Acarbose and miglitol are competitive inhibitors of alpha-glucosidase and modulate the postprandial digestion and absorption of starch and disaccharides. Miglitol differs structurally from acarbose and is six time more potent in inhibiting sucrase. The binding affinity of the two compounds differ, acarbose and miglitol

both target alpha-glucosidases: sucrase, maltase, glycoamylase, dextranase. Isomaltase and Beta-glucosidase are targeted only by miglitol and alpha-amylase only by acarbose. The clinical consequence of enzyme inhibition is to minimize upper intestinal digestion and absorption of ingested starch and disaccharides in the distal small intestine, lowering postmeal glycemic excursions and creating an insulin-sparing effect (Nolte and Karam, 2001). Prominent adverse effects include flatulence, diarrhoea, and abdominal pain, which result from the appearance of undigested carbohydrate in the colon that are then fermented into short-chain fatty acids, releasing gas (Nolte and Karam, 2001).

3.2 Introduction of Depression:

Depression is a condition characterized by symptoms of sadness, loss of interest/pleasure, guilt/low self-worth, disturbed sleep/appetite, low energy, changes in movement (agitation/slow movements), poor concentration and thoughts of death/suicide. Depression can be long-lasting or recurrent, with half of those affected experiencing more than one episode (Patten & Juby et al. 2008). It can substantially impair an individual's ability to function at work or school or cope with daily life. Depression can also decrease a patient's ability to manage their other chronic conditions.

Depression Risk factors:

Table Number:

Risk Factor	Nature of the Association
Age	First episode of depression is typically between the ages of 20 and 40, with middle age adults most at risk
Sex	More women than men develop depression and attempt suicide more frequently, but men are more successful in suicide attempts
Family history	Having a family member with depression or other mental illness increases the risk of depression
Race/ethnicity/culture	Depression affects adults in all populations, but Jewish people may be more likely and Asian and Blacks less likely to be depressed. Cultural differences may also impact the ways in which people express their feelings and their willingness to seek treatment.
Socioeconomic status (SES)	Low SES adults may be at increased risk, but depression affects people of all education and income levels
Residence	Urban residents are more likely to be depressed than in rural
Marital status	Depression may be highest in divorced, widowed or never-married adults and lower for those married, but this association may pertain more to men than women
Employment status	Unemployed adults are at increased risk of depression
Smoking	Increased tobacco use has been linked to depression
Alcohol	Increased alcohol use has been linked to depression
Negative early childhood experience	Early childhood trauma, such as loss of a parent before adolescence, child neglect, physical, emotional or sexual abuse, and parental divorce are linked to increased risk for adult depression.
Stress	Negative life events and chronic stresses, such as divorce, loss of a loved one or loss of employment are associated with increased depression.
Chronic physical conditions	Adults with chronic physical illnesses such as obesity, sleep disorders, osteoarthritis, Parkinson's, dementia, Epilepsy, thyroid disorder, hormonal imbalances, microbial infections, cancer and cardiovascular diseases are at increased risk of depression
Mental health conditions	Adults with other serious mental disorders such as schizophrenia and anxiety are at increased risk of depression
Medications	Certain medications cause depression-like symptoms such as sedatives and pain medications

Adapted From: (Haggerty et al. 2006).

Diagnosis of Depression:

The criterion standard for diagnosing clinical depression varies with the setting and depends on the information available. In secondary or tertiary care settings this is a structured diagnostic interview with a mental health professional (First, Spitzer, Gibbon, & Williams, 2012). Simple patient self-reports have been used as the criterion standard against computer algorithms in large databases for depression validation (Frayne et al., 2010). However, self-assessment alone involves inaccuracies as patients may be unaware of their problems or deny them, and there is no opportunity to incorporate that information in the assessment as with clinical tools where the family physician's opinion is also solicited. Conversely, the burden of long instruments may compromise participation rates (Aalto, Elovainio, Kivimäki, Uutela, & Pirkola, 2012; Pibernik- Okanovic, Peros, Szabo,

Begic, & Metelko, 2005) and they may be unnecessarily detailed and invasive causing more severely patients with depression to be less inclined to complete them (Pouwer et al., 2010, 2011).

Elderly, male patients in particular tend to refuse the Composite International Diagnostic Interview, leading to selective non-response bias possibly related to the burden and stigma surrounding mental health care (Pouwer et al., 2010). The more cumbersome Composite International Diagnostic Interview goes into great detail to distinguish between different types of depression which is not necessary in a diabetic context as all types of depression, even sub-threshold levels, may put patients at an elevated risk (Chiu et al., 2010). In the primary care setting validation of depression is difficult. As Kessler states, "no highly reliable and valid clinical gold standard is available" (Kessler et al., 2004, page 136). Interviews with family physicians have many advantages such as the ongoing relationship with the patient, the full history in the patient's chart and the ability to order additional tests and review medications, however many cases of depression still do not come to medical attention (Kahn et al., 2008; Katon et al., 2004; Sartorius et al., 1993). Screening for depression with a brief questionnaire is a potential solution as facilitating family physicians in identification and management of depression can improve patient outcomes (Tiemens et al., 1999).

The Patient Health Questionnaire-9 question version (PHQ-9) is the most widely used major depression screening scale (Kessler et al., 2013) and is not only a screening tool for depression, but it is used to assist primary care physicians in diagnosing depression (Kahn et al., 2008). Using a mental health professional interview as the criterion measure, the accuracy of PHQ-9 >9/27 scores at detecting depression was assessed in 6000 primary care and obstetrical patients. This validation work found a sensitivity of 88% and a specificity of 88% for Major Depressive Disorder for the dichotomized PHQ-9 score (Kroenke, Spitzer, & Williams, 2001). Patients at this threshold (>9) more likely to receive a depression diagnosis. Those below the threshold of 5 only had a 1 in 25 chance of truly

having depression. Scores of 5, 10, 15 and 20 represented mild moderate, moderately severe and severe depression, respectively (Kroenke & Spitzer, 2002).

The PHQ-9 provides information on depression severity as well and picks up on more severe disease better than other tools (Meader et al., 2011). In a 2012 meta-analysis of screening tools for depression in diabetes the Beck Depression Inventory was the most cited, but the prohibitive costs of annual licensing fees, data record forms and manuals may explain its rare use in clinical practice (Bauer & Shanley, 2006). Due to its open access, the lack of cost makes it an appealing option for primary care and it is the recommended tool in the British Columbia depression screening guidelines (Roy, Lloyd, Pouwer, Holt, & Sartorius, 2012). The PHQ-9 also has been specifically validated in a population with diabetes and/or coronary heart disease resulting in a sensitivity of 84% and specificity of 82% against the Mini Neuropsychiatric interview (Zwaan & Dijk, 2016). These investigators also found it performs well at identifying those at high risk for depression, but that further diagnostics are recommended to identify Major Depression. For research purposes, reasonable response rates have been observed when the PHQ-9 has been mailed out with a letter signed by the patient's family physician (Baas et al., 2009). As diagnosing depression can be difficult, and the information available in a patient's medical chart may be insufficient to accurately categorize depression status, adding screening tools like the PHQ-9 into the physician evaluation process is critical.

Depression Treatment:

Depression treatment can be effective and generally consists of antidepressants and/or psychosocial therapy depending on treatment responses, condition severity and patient preferences (Canadian Network for Mood and Anxiety, 2014; De Jonghe, Kool, Van Aalst, Dekker, & Peen, 2001; Ministry of Health, 2013; Parikh et al., 2009; The College of Family Physicians of, 2003). For patients who do receive some form of mental health care, there are still large gaps between the treatment they received and what the clinical guidelines suggest they should receive (Duhoux, Fournier, Nguyen, Roberge, &

Beveridge, 2009; Fernández et al., 2006; Fortney, Rost, Zhang, & Pyne, 2001; Hepner et al., 2007; Hirschfeld et al., 1997; Kohn, Saxena, Levav, & Saraceno, 2004; Patten, 2001; Sewitch, Blais, Rahme, Bexton, & Galarneau, 2007; Slomp et al., 2009; Starkes, Poulin, & Kisely, 2005; Stephens & Joubert, 2001). The World Health Organization found mental health treatment gaps and lag time need to be decreased in all countries (Kohn et al., 2004).

3.3 Diabetes and Depression:

Prevalence of Depression in Diabetes:

Many factors influence the prevalence of depression among those with diabetes. In the Netherlands, 2,460 patients with type 2 diabetes were examined for depression and 26% met the criterion standard for depression (Nefs, Pouwer, Denollet, & Pop, 2012), but those with any previous history of depression had increased recurrent or persistent depression. In 2001, researchers from the US Department of Veterans Affairs Medical Center performed a meta-analysis to estimate the odds and prevalence of clinically relevant depression in diabetes, and found the presence of diabetes doubles the odds of having comorbid depression (Anderson, Freedland, Clouse, & Lustman, 2001). Investigators also showed the prevalence of comorbid depression was significantly higher in clinical (32%) than community samples (20%) and when assessed by self-reported questionnaires (31%) vs standardized diagnostic interviews (11%).

Researchers at the University of Birmingham completed a meta- analysis of the risk of developing depression and found that those with type 2 diabetes have higher chances for developing depression as defined by diagnostic criteria (Nouwen et al., 2010). Overall, it appears that approximately one out of every three patients with diabetes also suffer from depression at some point in their lifetime and this could interfere with the control over diabetes (Anderson et al., 2001; Nefs et al., 2012; Pouwer et al., 2010).

Effect of Depression on Mortality in Diabetes:

Researchers have concluded that diabetes and depression can potentially be a "lethal combination" (Katon, Jürgen, & Pincus, 2008). People with diabetes have a doubled risk of depression, yet most concerning in a Cox proportional hazard model, having depression and diabetes was associated with an almost 40% increased risk for all-cause mortality over a 2yr period compared to having diabetes alone (Katon, Jürgen, & Pincus, 2008). However research is still needed to determine whether this increase in mortality associated with depression is due to potential behavioral factors (smoking, poor adherence to diet) or physiologic abnormalities (hypothalamic-pituitary adrenal axis dysregulation) associated with depression.

Effectiveness of Depression Treatment in Diabetes:

Providing adequate depression treatment has been shown to improve glycemic control. In the US Health and Retirement Study, highly depressed subjects demonstrated significantly higher HbA1c levels at 5 year follow-up compared to those with little or no depressive symptoms (Chiu et al., 2010). The University of Pennsylvania conducted a randomized controlled trial of 180 people with depression and diabetes evaluating an integrated care intervention aimed at educating primary care physicians on guidelines for depression treatment and monitoring of patients. Investigators showed that after 12 weeks the proportion of patients achieving glycemic control (HbA1c<7) was 60.9% for the depression intervention group, but only 30.7% for the usual care group ($p< 0.001$) (Bogner, Morales, de Vries, & Cappola, 2012). The intervention group also showed higher rates of adherence to oral hypoglycemic and antidepressants, as well as a greater portion achieving depression remission defined as PHQ-9 <5. The usual care group had fewer numbers of visits and this may have mediated the outcomes. Similarly in a Washington State randomized controlled trial monitoring depression symptoms in 14 primary care clinics involving 214 patients with poorly controlled diabetes, coronary heart disease or both in addition to co-morbid depression, after 1 year 36% of the collaborative care

depression intervention group had a reduction from baseline blood sugar levels of ≥1% while only 19% of the usual care group did (Katon et al., 2010). Overall, the depression intervention group had significantly improved depression scores and achieved greater reduction in HbA1c levels, which is both a highly statistically significant and clinically relevant reduction on a population level. However, other studies have shown an association with glycemic control and depressive effect is present only in type 1 not type 2 diabetes (Pouwer et al., 2010) and that depression screening intervention not directly linked to treatments may not convey the benefits on glycemic control (Pouwer et al., 2011).

Screening for Depression in Diabetes in Primary Care:

Managing depression begins by physician recognition, however many patients' chronic conditions may have depression not detected in primary care. As such National Institute for Clinical Excellence (NICE) guidelines recommend using a validated assessment tool for this purpose (National Institute for Clinical Excellence, 2004). The Patient Health Questionnaire-9 question version (PHQ-9) is a common choice in primary care as it categorizes a greater portion of moderate/severe depression than other tools (Cameron, Crawford, Lawton, & Reid, 2008; Kroenke & Spitzer, 2002). Gaining a better understanding of the dual impact of having both diabetes and depression and their optimal primary care management is essential. The screening tools used need to be evaluated in patients with diabetes specifically since these patients are known to be at increased risk. The routine use of effective tools may assist family physicians in the recognition and treatment of both conditions. The relationship between diabetes and depression was examined in a New York State study of 249 diabetic Medicare patients who were screened for depression using a mailed Patient Health Questionnaire (PHQ-9). Then they were further clinically assessed resulting in 56% positive screens (PHQ-9≥ 10) for depression, with nearly half (49%) unrecognized by the health care system (Kahn et al., 2008). The other 51% with a diagnosis of depression in their medical encounter records still had

moderate to severe depression scores, suggesting both poor treatment adherence rates and a need for therapy reassessment. A similar PHQ-9 screening study in nine Washington State primary care clinics also found only 51% of diabetic patients with major depression were recognized as depressed by the medical system (Katon et al., 2004).

Causal Pathways between Depression and Diabetes:

The exact cause responsible for high prevalence of depression in depression and its effects on outcome is not well understood. However biological factors, psychological factors and their interaction are proposed to be causative agents for explaining this mechanism. Recent work on pathogenesis of depression-depression link has proven multiple interconnected mechanisms (Eaton et al. 1992, Brown et al. 2004) These include metabolic programming at genetic level and early childhood and utero nutrition, changing life styles both individually and collectively induce hyperactivity of HPA axis (hypothalamic-pituitary-adrenal axis). The end results in sympathetic nervous system activation and long standing hyper cortisolaemia is suggested to be for its distinct process. It includes activation of cell-mediated immune response, accumulation of visceral fat and insulin resistance, which ultimately progresses to DM (Webber-Hamman et al. 2002).

Depression is likely to play role in several ways of pathogenesis. First as a coincidental consequence of same environmental factors, that influence glucose metabolism. Second as an independent factor that also affects nutrition and life style behavior. Third as an phenotype of stress related disorders which have unifying over activation of HPA and inflammatory response to stress and as a marker of severity of underling pathogenesis of diabetes. Over all, the evidence is pointing towards depression –diabetes link, having to some extent a common origin in which some individuals are more vulnerable and programmed such that there is over activation of those stress regulation pathway which contribute to metabolic dysregulation (Adriaanse et al. 2006).

Depression and insulin resistance

The continuum of diabetes stretches from developing insulin resistance to impaired glucose intolerance and frank diabetes occurs as insulin secretion fails. Insulin resistance is regarded, as the fundamental step connecting depression to diabetes and varied pathways exists in these mechanisms. The activation of hypothalamic- pituitary adrenal (HPA) axis occurs in 40-60% of patients with major depressive disorder. Further causing increasing levels of cortisol and causing disturbances of gluco regulatory mechanisms. The end result is hyper insulinemia and insulin resistance, eventually leading to frank diabetes. Changes in lifestyle factors associated with depression also increase the risk of developing insulin resistance. Obesity is a common pathway and is a significant risk factor for increasing both insulin resistance and diabetes (Adriaanse et al. 2006, Anagnostis et al. 2009).

There are meta-analysis of nine prospective epidemiological studies, which showed that depression is associated with an increased risk of type 2 diabetes .The first observational study was done by British Women's and Health study of 4286 women aged 60-79 years randomly selected from primary care. The association was between two disorders was almost U shaped, with prevalence of depression decreasing linearly with increasing insulin resistance among women without diabetes and increasing among women with diabetes (Lawlor et al. 2003). It was reported that depression was inversely related to insulin resistance among 4,268 British women aged 60-79 years (Lawlor et al. 2003).

In a cross-sectional study comprising have 491 male and female patients. The study-enrolled individuals aged 61–63 years and reported that insulin resistance and severity of depressive symptoms were positively correlated, particularly in people with IGT (Timonen et al. 2005). However, these studies are in contrast with another study, which, concluded that reduced depressive symptoms are not associated with insulin resistance among 2,512 Welsh men aged 45-59 years (Lawlor et al. 2005).

Inflammation, insulin resistance and diabetes:

Recent research has shown that there is increased evidence between chronic inflammation and insulin resistance. There is also a growing body of consensus over the last decade on characteristics of inflammation in obesity and the mechanisms by which this inflammation contributes to insulin resistance. It is now suggested that inflammation in diabetes and insulin resistance occurs through inhibition of insulin receptor signalling pathways (Hotamisligil et al. 1994). Among the proinflammatory cytokine TNF-a mediate insulin resistance as a result of obesity in many rodent obesity models. Chemokine monocyte chemo tactic protein-1 (MCP-1) is another newcytokine proposed for impair adipocyte insulin sensitivity (Moller et al. 2000).

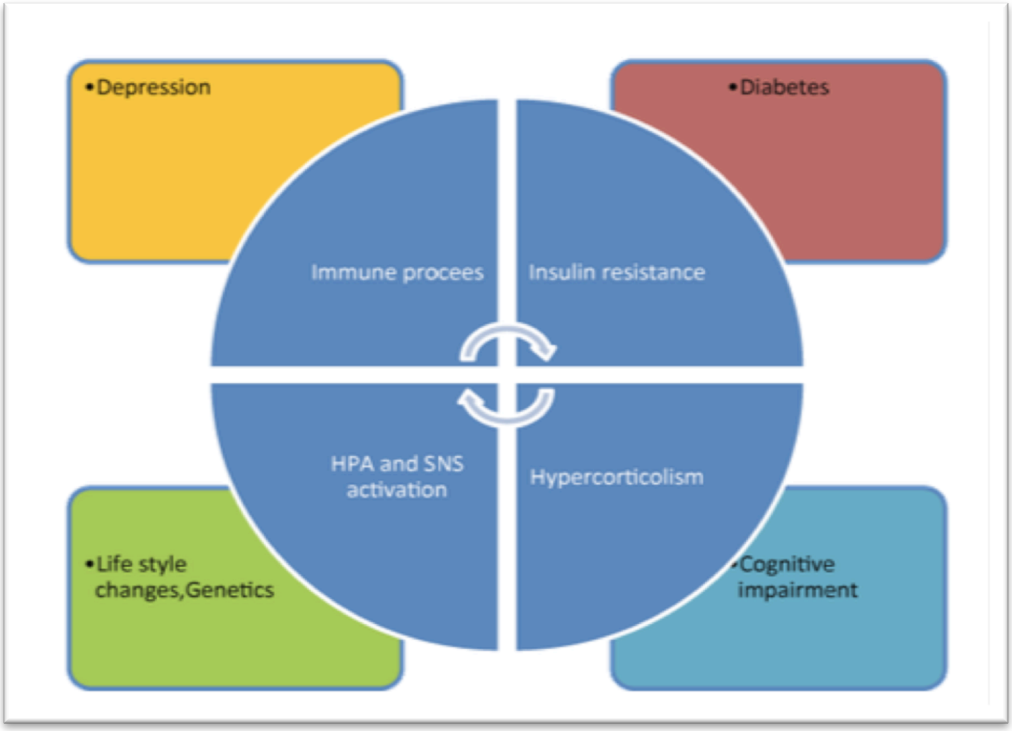


Figure 3.8 Inflammation, insulin resistance and diabetes

Sleep Disruption:

Difficulties sleeping, either too much or too little, are classic symptoms of depression and increase the risk of suicide (Nutt, Wilson, & Paterson, 2008). Sleep apnea is a known risk factor for the development of diabetes (Wang et al., 2013). Altered circadian rhythms, especially short sleeping, have been shown to impair glucose regulation, increase insulin resistance, and the risk of diabetes onset (Mallon, Broman, & Hetta, 2005; Yaggi, Araujo, & McKinlay, 2006). Disruption of quality sleep patterns provides another potential physical link between these two chronic conditions (Holt, de Groot, & Golden, 2014; Snoek et al., 2015).

General dysregulation of physiological systems and neuroendocrine alterations of the hypothalamic pituitary adrenal axis, autonomic nervous system, immune system, glucose transport systems or circadian rhythms could manifest themselves as both symptoms of depression and diabetes (Lett et al., 2004; Musselman et al., 2003).

Indirect Psychosocial, Environmental and Behavioural Mechanisms:

Chronic Condition Burden:

Direct biological pathways likely contribute to depression in diabetes, but it could also be partly explained by the psychological stress from the burden of living with a demanding chronic condition and its debilitating complications. The daily demands of having to cope with fluctuating blood sugar levels, continuously needing to balance insulin dosages, self-administer injections, maintain regular oral medication compliance, relentless daily physical activity requirements, scrutinizing food for low glycemic options, and worries about hypoglycemia could cumulatively lead to a unique form of emotional distress for patients with diabetes. Evidence for this pathway is provided by a 2011 meta-analysis using psychiatric interviews, self-reported questionnaires and physician diagnosis as the depression criterion standard to examine any potential associations in glucose impairment and undiagnosed diabetes. Investigators only observed associations with depression in

those with previously diagnosed diabetes, supporting the "psychological burden hypothesis". This states that the burdens of a diagnosis of chronic illness like diabetes that must now be managed daily and coping with its complications are what contribute to high levels of depression (Nouwen et al., 2011).

Lifestyle and Behavior:

It is easy to hypothesize that lifestyle factors could be involved in the comorbidity of depression and diabetes, with either condition reinforcing the other. If depression is not adequately addressed it may be difficult for the patient to find the motivation to adhere to their diabetes self-care regimen and medications (McKellar, Humphreys, & Piette, 2004). Patients with low levels of activation are less likely to play an active role in maintaining health. They are less likely to seek needed help or follow advice of their health providers. Lack of confidence and experience failing to properly manage their health may result in avoidance of health problems and general self-neglect. Essentially in the model of effective chronic illness care, not only is providing patients with high quality information about how to manage their condition important, they must be in an "active" state in order to act on that information. Depression can directly inhibit a patient with diabetes' ability to be effectively engaged even in the best-prepared, proactive treatment program. They may have diminished compliance with taking their prescribed diabetes or depression medications, checking their blood sugar levels, attending the medical appointments or participating in their recommended diet and exercise regimes. Identifying and supporting an "inactive" patient with diabetes is critical to successful long-term control over blood sugar levels.

Certainly even mild physical activity such as walking can directly and immediately reduce blood sugar levels in diabetes (DiPietro et al., 2013). Exercise also has a positive impact on mood repair and so is beneficial for both conditions (Craft & Perna, 2004). There is evidence that lifestyle and health behaviours play a role in this comorbidity. High BMIs or obesity are known to put patients both at risk for depression and diabetes (J. A. Bell et al.,

2014; Freemantle et al., 2008; Luppino et al., 2010). Similar to Pan's US estimates, a large Chinese study involving half a million people demonstrated that major depression was associated with diabetes and the relationship was strongest among those who were not obese. This supported their "jolly fat hypothesis" which is that there is an inverse relationship between depressive symptoms and weight found primarily in Asian populations. This is inconsistent with the Western hypothesis that BMI mediates the diabetes-depression relationship, suggesting culture may also be a determinant (Mezuk et al., 2013). However this has also been shown to be a bidirectional relationship, as depression increases the chances of future obesity and diabetes (Pan et al., 2011, 2010).

Environment:

The risks of depression and diabetes can be affected by environmental factors ranging from intra-uterine elements on the developing fetus to local residential neighborhood dynamics on the grown adult. Although the findings demonstrate mixed results, some investigators have suggested that maternal stress causes an overexposure to cortisol and catecholamines on the developing fetus. As a result, long-term alterations in the neuroendocrine system may be initiated that predispose a child to both depression and diabetes (Phillips, 2007). Adverse neighborhoods and schools with decreased walkability and high traffic, as well as those with poor social environments like those with low cohesion and high violence, have been linked to negative dietary behaviours and decreased physical activity levels which could make a person more vulnerable to depression and diabetes (de Vet, de Ridder, & de Wit, 2011). The direct and indirect causal mechanisms between depression and diabetes are considerably complex with many factors so interrelated they are likely to exacerbate the symptoms of one another.

Impact of Depression on Diabetes:

The co morbid diabetes and depression is associated with significant morbidity as well as mortality, therefore focusing and treating depression is very important and needs special

attention (Kohen et al. 1998, Goldney et al. 2004). There is a close relationship between distressing life events in diabetic and period of diabetic control, which may even lead to development of ketotic coma. Patients treated for diabetes have higher chances of developing depressive symptoms, during follow up period. Further, when depressive symptom occurs, they are associated with poorer adherence to diabetic diet, poorer compliance to drugs, complications and impairment in function (Goldney et al. 2004, Ciehanowski et al. 2000). This fact is supported by at least 3 randomized control trials. The three trials have shown that treatment either with antidepressants or cognitive behavior therapy results in improvement in glycemic level as well as mood symptoms. Whatever the underlying exact causes are, depression may have an important bearing on course of diabetes, leading to worsening of diabetes control and increased complications. Effective treatment facilitates compliance to diet and exercise and results in improving glycaemic control (Lustman PJ et al; 2000, 1998, 1997).

Management of depression and diabetes:

The proper management of depression in individuals with diabetes depends on integrated treatment as well as overall care of the patients. There is a general consensus of close relationship between depression, diabetes and further each of these two conditions can effect patients overall health and course of the disease (Katon et al. 2003). This is also supported by bidirectional relationship of depression and diabetes as each condition may increase the both risk and severity of other condition (Golden et al.2008). There is also the cost of care related to diabetes and depression is also greatly increased through the interaction of both two disorders. The effect of depression on management of diabetes is vast and complex. Depression affects quality of life and thus affects the life style activities, leading to changes in self-monitoring and medication usage. The cognitive dysfunction in depression patients also adds to the complexity of care and cost of care (Van der Feltz-Cornelis et al. 2010, Munshi et al. 2006). Depressions in diabetic patients have higher levels and increased severity of symptoms leading to more prolong.

Thus successful management of both disorders depends upon on integrated cooperation between different branches of medical sciences for optimal results for these disorders (Munshi et al. 2006).

Varied factors influence treatment of depression in diabetes. Effective non-pharmacological interventions such as regular exercise for depression, Cognitive behavioral therapy and psycho education should be offered (Otto et al. 2005). Diabetics' patients suffering from mild depression, the initial treatment to offer is support to patient and their families followed by information regarding diseses. Problem solving therapy, cognitive therapy or interpersonal psychotherapy can be used in patients with moderate depression (Otto et al. 2005, Popkin et al. 1985)

Antidepressants and Diabetes mellitus:

Antidepressants increase the risk of DM up to two fold. This risk is associated with both with tricyclic antidepressants and selective serotonin inhibitors (SSRI) and varies with duration of use of antidepressants. Antidepressant treatment for shorter periods or with lower daily doses was not associated with an increased risk (Kiwim et al. 2010, Lustman PJ et al. 1997). Treatment of depression with selective serotonin reuptake inhibitors may improve glycemic control and may be beneficial for these patients. Among SSRI'S, Fluxetine has been shown to improve in HbA1c, decreases insulin requirements , loss of weight and increases insulin requirements. TCA causes increased weight gain, hyperglycemias and increased appetite (Maheux et al. 1997). Among TCA's nortrypline improves depression but worsens glycemic control in diabetes in study (Lustman PJ et al. 1997). SSRI's does not disturb glycemic control and has seen has very less effect on weight gained and glycemic level. Among SNRI'S, dulextine has shown to no influence on glycemic control. Limited data are available on venlafaxine (Raskin et al. 2006). Although mirtapine is associated with weight gain, little data is available which shows its effect in diabetes. There is no data currently available with trazadone and robextine (Himmerich et al. 2006).

Protective measures:

A multidisciplinary team approach, including an endocrinologist, diabetes training, and mental health practitioner, is ideal for the treatment of depression in DM. Depending on the severity of the comorbid psychopathology; a psychiatrist may also be needed for psychopharmacological evaluation and treatment (Lustman PJ et al. 2000). Early on in treatment, intensive glycemic management of diabetes is an appropriate target for a person with diabetes and comorbid depression. The first goal should focus on medical stabilization. Psychiatric interventions like education, counseling and treatment could be the missing link in the overall management of the patients suffering from diabetes mellitus (Lustman PJ et al; 2000, 1998).

Chapter 4

Materials & Methods

4.1 Research setting

The study was carried out in Dia-care diabetes and hormone clinic. Dia-care is the tertiary care clinic located in Ahmedabad. Patients were recruited from the clinic on the everyday basis.

4.2 Human subject ethical approval

Study approval was obtained from the institutional ethics committee, for formal review and approval of the study conduct. Case report form (CRF) and informed consent form (ICF) were also submitted to for ethics committee for approval. Institutional Ethics Committee (IEC), Nirma University, approved the study protocol. Protocol Number. IEC/NU/18/IP/03

4.3 Study Technique

This was single centric observational study and it had prospective component. Participants were selected randomly from the waiting area and likewise. A pre-designed; pre-tested questionnaire was used for data collection. The subject explained the questions properly to avoid any form of misunderstanding and facilitate accurate response.

The questionnaire was used to get patient social, demographic information included age, gender, marital status, education level, occupation. Information about type and duration of diabetes, HbA1c level, family history and comorbidities along with diabetes were also recorded from the participants. The questionnaire was available in two languages: English and Gujarati. Case report form was only available in English.

Weight was measured by using a weighing machine that measures in kilograms (kg) and height was measured in centimeter (cm) and BMI indices (Knowles et al. 2010, Arora et

al. 2014). Subjects need to remove their belongings such as shoes, mobile phones, bag, wallets, and watch.

Body Mass Index (BMI) calculated by weight in kilogram (kg) divided by height in meter square. BMI (kg/m2) was classified as: Underweight <18.5, Normal range 18.5 – 24.9, Overweight 25.0- 29.0 and Obese ≥30.0 (Knowles et al. 2010, Arora et al. 2014).

Blood Pressure (BP) measured by sphygmomanometer in a seating position. BP was measured in millimeter of mercury (mmHg) twice with the 5 minutes difference. Normal BP was less than or equal to 130/80 mmHg according to JNC guideline (Aram et al. 2004).

HbA1c is used to measure average blood glucose level and it provides an idea of how well diabetes been controlled over last 2-3 months. It is the gold standard of care for determining the potential risk for developing comorbidities like renal disease, cardiovascular disease, neuropathy or stroke (ADA,2010). Higher chances of potential complications if HbA1c remains increased for a longer period of time. The normal level of HbA1c in human is generally <7% (ADA, 2010). HbA1c was obtained on the same day at the study site before or after completing the questionnaire.

Assessment of Depression was defined by using the validated PHQ-9 tool, The study was graded subjects with no depression with score 0, Minimal 1-4, Mild 5-9, Moderate 10-19 and severe 20-27. (Kroenke et al. 2001 & 2002)

4.4 Study Duration

January-2018 to April-2018

4.5 Sample Size

The sample size is estimated based on the prevalence of depression among diabetic patients of 38.75 % (p=0.38) from Aligarh, India (A. Mushtaque, 2016). The exact sample size was calculated by using a formula for single population proportion by assuming 5%

precision (d), 95% confidence interval (CI). Based on the above information the total initial sample size was calculated by using the following formula (Kish Leslie formula, 1965).

$$N = Z^2 P (1-P) / d^2$$

Where:

N = Sample Size

Z = Standard normal deviate (1.96) for 95% Confidence Interval

P = Prevalence of depression among diabetes was 38.75 %

d = Precision 0.05 (d = 5%)

Sample size obtained was **N**= 360

4.6 Sampling Criteria

4.6.1 Inclusion Criteria

- A diagnosed case of diabetes.
- Patient age >18 years
- Duration of diabetes >1 year.
- Subjects who were willing to participate in the study

4.6.2 Exclusion Criteria:

- Patient age <18 years
- A patient who is not willing to sign the consent form
- A patient who doesn't understand the questionnaires or deaf or not able to answer is excluded.

4.6.3 Data Collection Tool

- Informed consent form (English and Gujarati)
- Case record form (English)
- Patient Health Questionnaire (PHQ-9) (English and Gujarati)

4.6.4 Evaluation Parameters

- Age
- Gender
- Level of Education
- Occupation
- Marital status
- Physical activity
- Body Mass Index
- Type of diabetes
- Duration of diabetes
- Family history
- Glycated Hemoglobin (HbA1c)
- Blood Pressure
- Micro – vascular complications
- Macro – vascular complications

4.7 Data collection and Analysis

Before the analysis, the data were coded to maintain the confidentiality of all the participants and maintain the very good flow throughout the study. To carry out the statistical analysis variables measurements were established. Demographic information was obtained to ease down the statistical analysis. Descriptive analysis was carried out for all the variables and noted as mean ± SD. Chi-square test and t – test was used to measure the strong association between variables and p-value <0.05 considered as statistically significant.

Chapter 5

Results

Gender wise distribution of diabetic patients:

There were total 360 participants in the study. Gender wise prevalence of diabetes was seen in one hundred and fifty-four participants (43%) female, and Two hundred and six participants (57%) male.

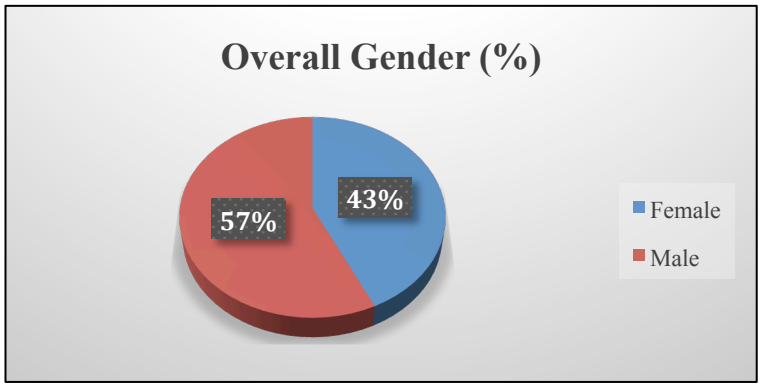


Figure 5.0 Gender wise distribution of Diabetes

5.1 The prevalence of depression:

The overall prevalence of depression among diabetic patients (N=360) was found to be (64.72 %). Among all 55.56 % were having mild depression, 7.78 % patients had moderate depression, 1.39 % participants had severe depression and 35.28% patients had reported with no depressive symptoms.

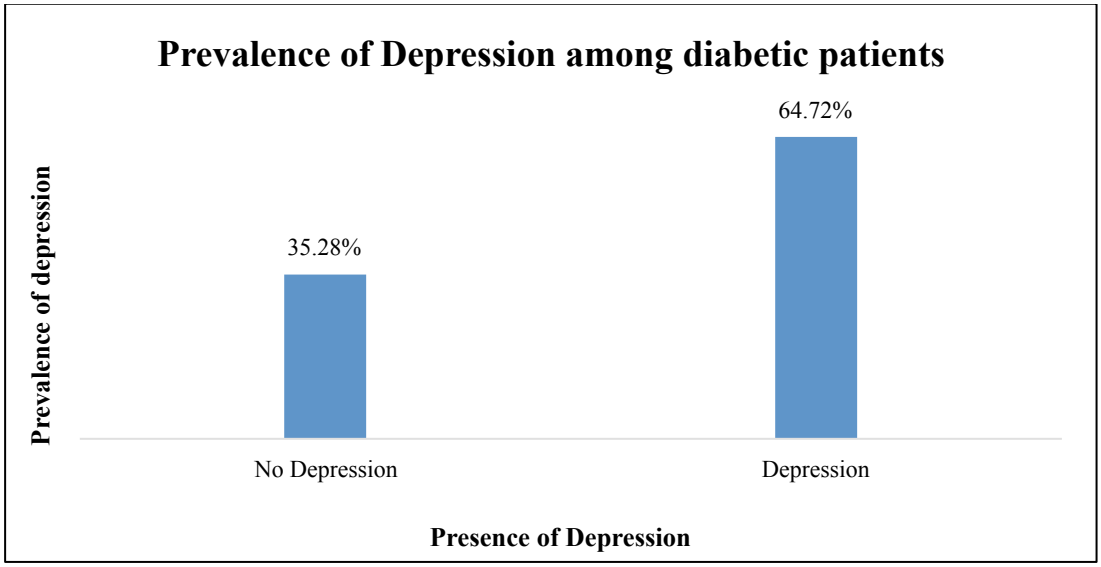


Figure 5.1 Prevalence of depression among diabetic patients

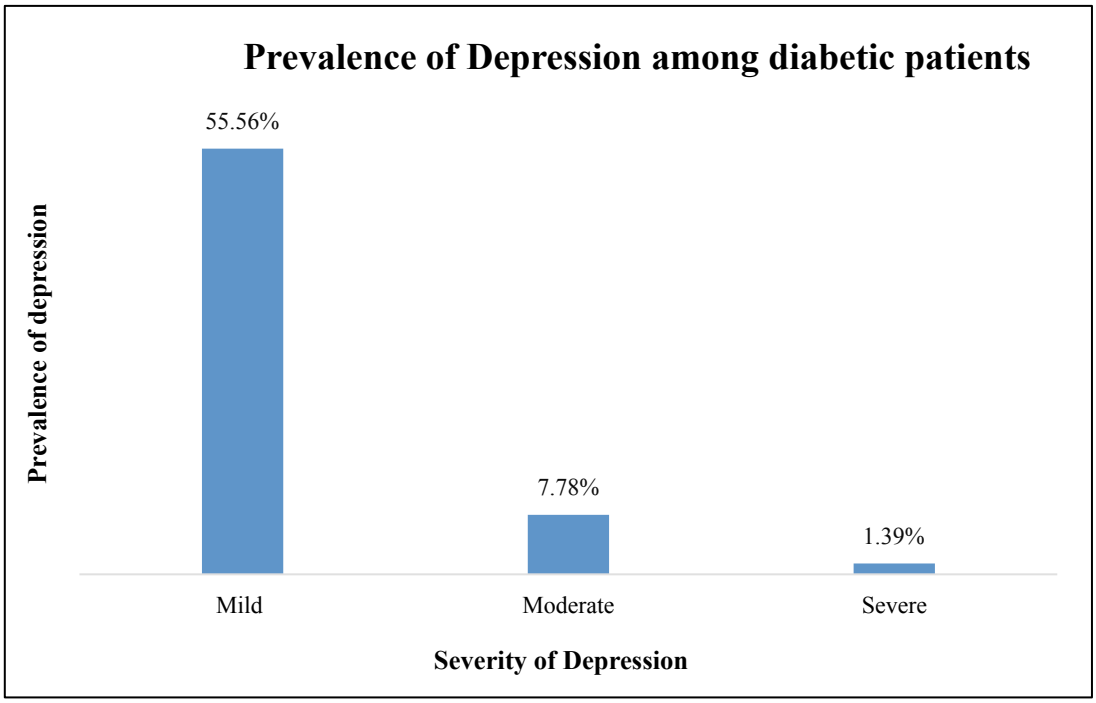


Figure 5.2 Severity of Depression diabetic patients

5.2 Age wise prevalence of depression in diabetic patients:

In the present study, the total 360 patients were enrolled, and 234 patients were found to have depression as per Patient Health Questionnaire (PHQ-9) score. The highest prevalence of depression was found in the age group of 61-80 (70.85 %). Present data show that there is a significant correlation between age and depression.

Table 5.1 Age wise prevalence of depression

Age	Diabetes without Depression		Diabetes with Depression	
	Total Number (N=127)	Percentage (%)	Total Number (N=234)	Percentage (%)
Less than 20 years	6	2.11	0	0
21 – 40 years	34	11.99	30	19.5
41 – 60 years	60	21.16	95	61.75
61 – 80 years	27	9.525	109	70.85

Table 5.2 Age wise comparison of prevalence of depression

Test	Value	df	P value	Statistically Significant (P< 0.05)
Chi-square	34.95	3	<0.0001	Yes

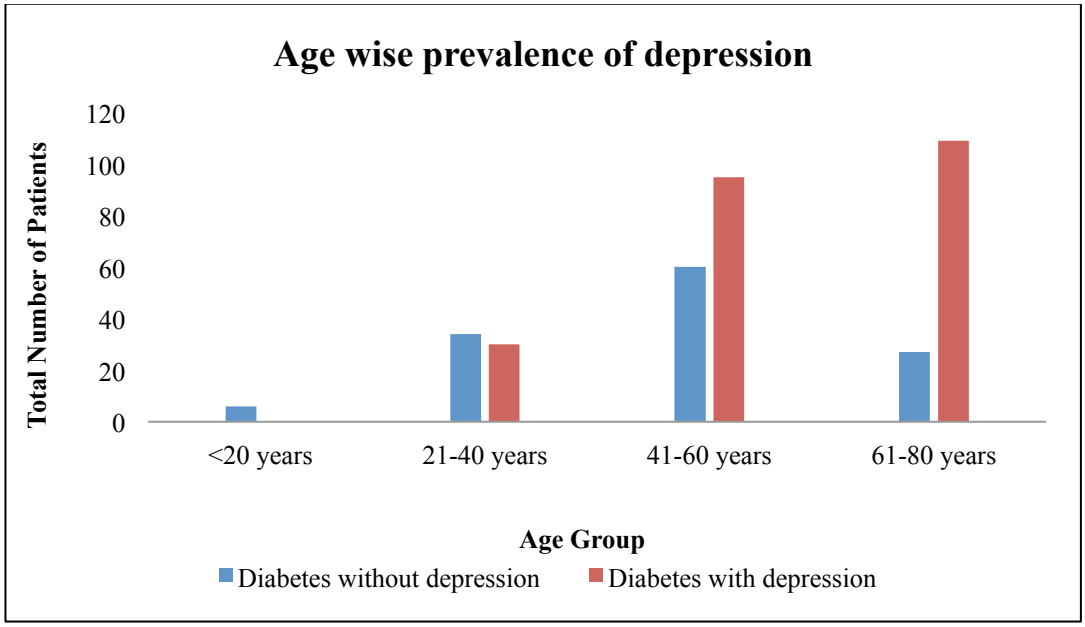


Figure 5.3 Age wise prevalence of depression

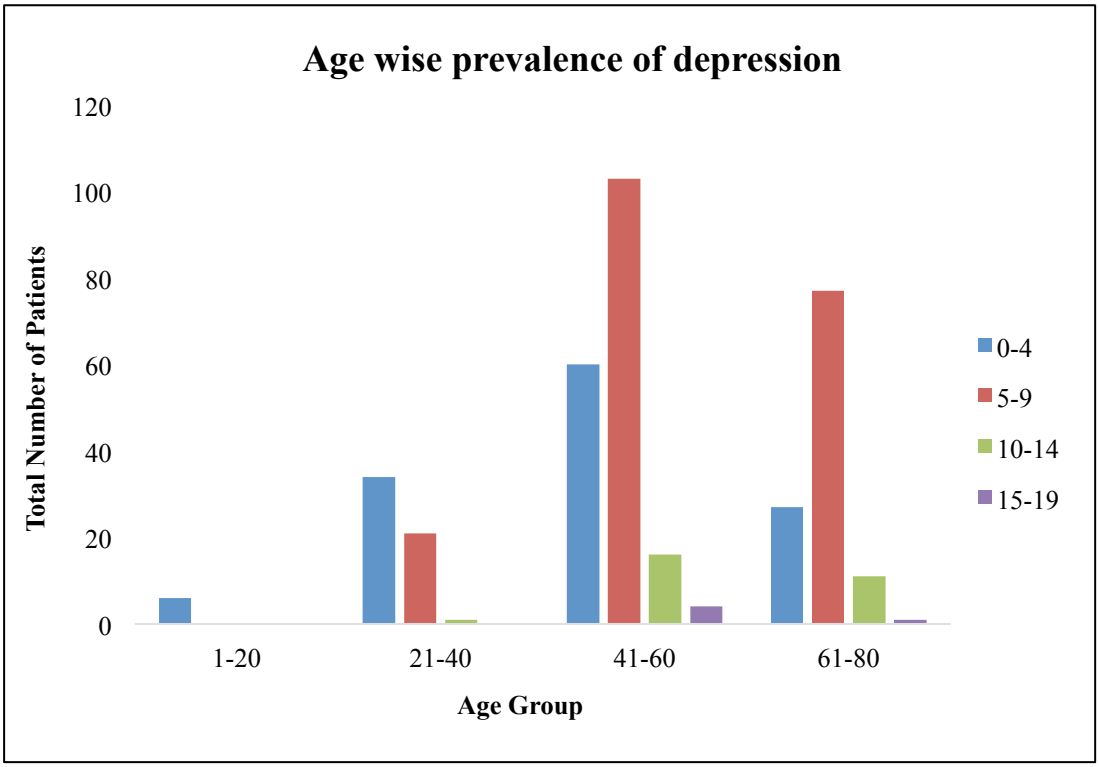


Figure 5.4 Age wise prevalence of depression (PHQ-9)

5.3 Gender wise prevalence of depression in diabetes patients:

The result shows the rate of prevalence of depression was in males (79.60 %) and females (71.19 %). Out of 360 participants, no signs of depression were seen in 83 males (29.28 %) and 44 females (15.52 %). Thus, gender was statistically significant while it was compared in both, diabetic patients with depression and those without it.

Table 5.3 Gender wise prevalence of depression

Gender	Diabetes without Depression		Diabetes with Depression	
	Total Number of patients	Percentage (%)	Total Number of patients	Percentage (%)
Male	83	29.28	123	79.60
Female	44	15.52	110	71.19

Table 5.4 Gender wise comparison of depression

Test	Value	df	P value	Statistically Significant (P< 0.05)
Chi-square	5.301	1	0.0213	Yes

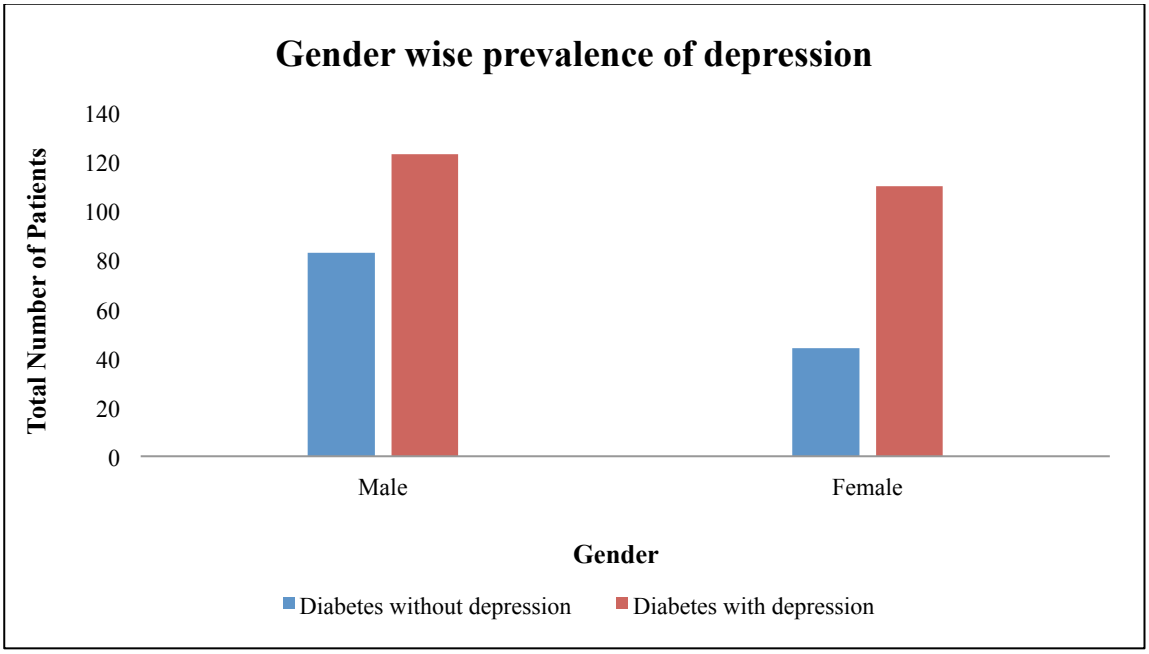


Figure 5.5 Gender wise prevalence of depression

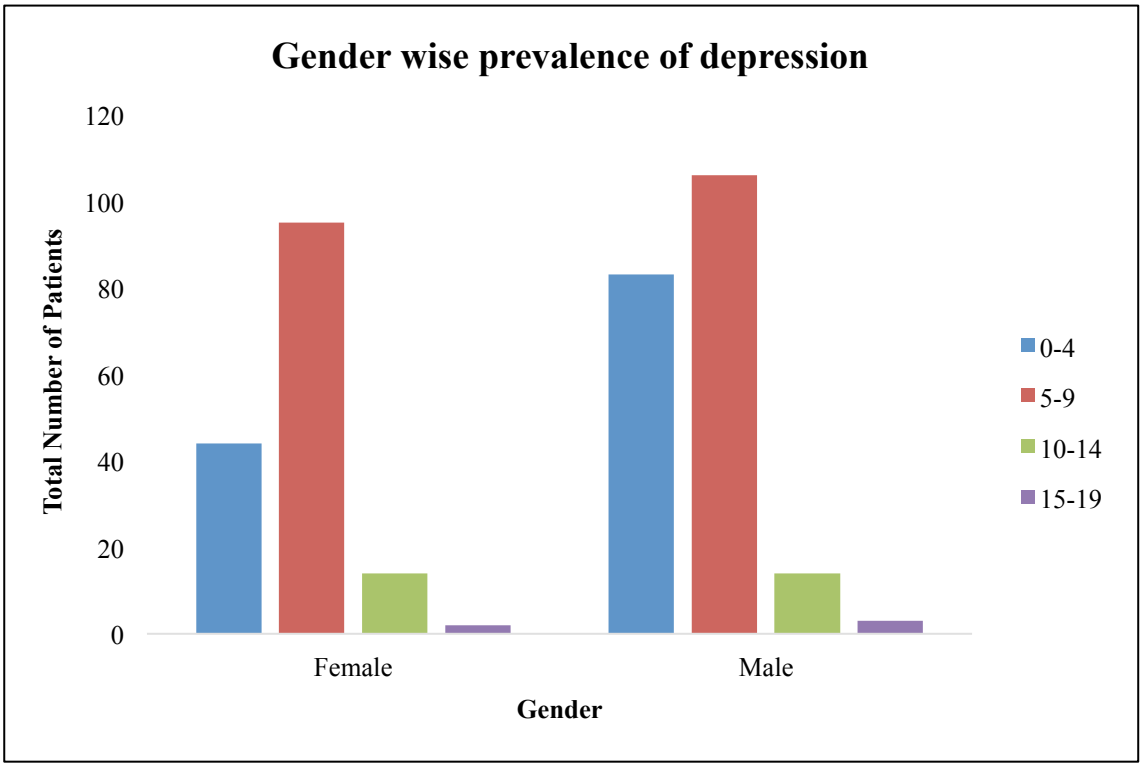


Figure 5.6 Gender wise prevalence of depression (PHQ-9)

5.4 Proportion of presenting symptoms among participants:

In this study, the PHQ-9 assessment score for depression showed that depressed mood and fatigue were the most common symptoms in the patients. Suicidal ideation was present in 3.30% of participants.

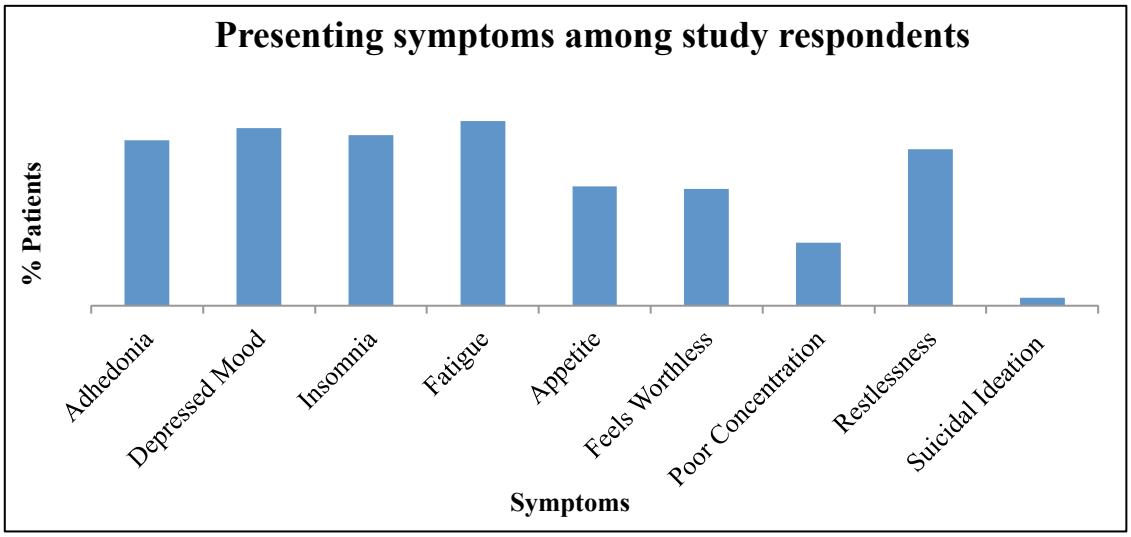


Figure 5.7 Presenting symptoms among study respondents

5.5 Prevalence of depression based on type of diabetes:

While comparing Type – I and Type – II diabetic patients in this study, it has been found out that majority of Type – II diabetic patients were suffering from depression (N = 225, 62.32%). There was significant correlation found between the type of diabetes and depression.

Table 5.5 Type of diabetes wise prevalence of depression

Type of Diabetes	Diabetes without depression		Diabetes with depression	
	Total Number of patients (N)	Percentage (%)	Total number of patients (N)	Percentage (%)
Type - I	13	3.60	9	2.49
Type - II	114	31.57	225	62.32

Table 5.6 Type of diabetes wise comparison of depression

Test	Value	df	P value	Statistically Significant (P< 0.05)
Chi-square	5.874	1	0.0154	Yes

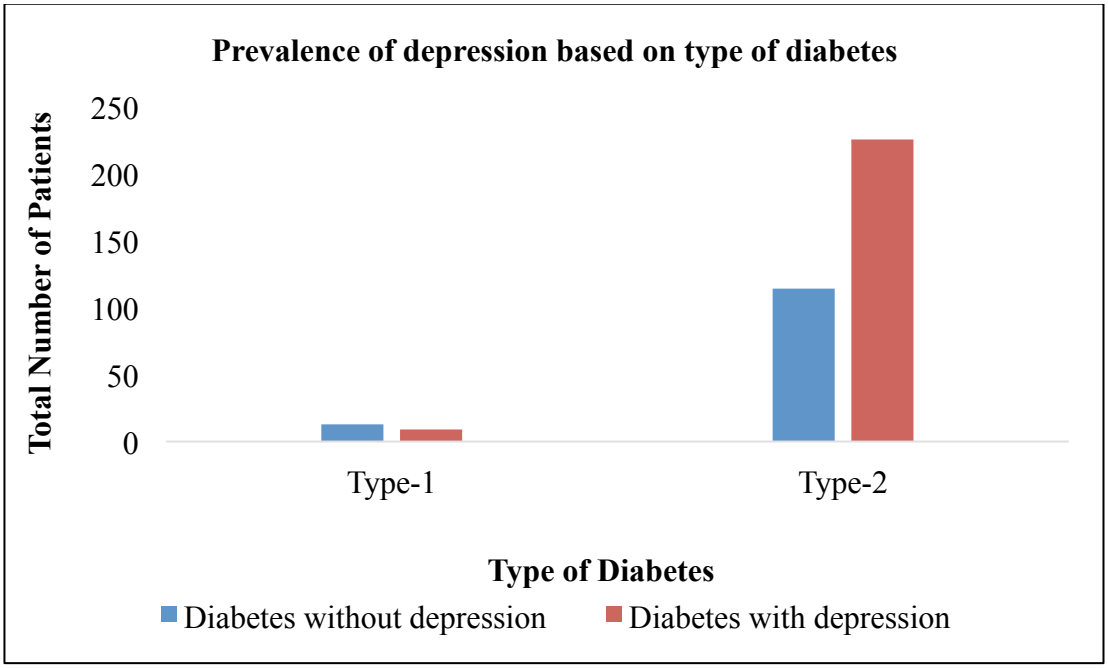


Figure 5.8 Type of diabetes wise prevalence of depression

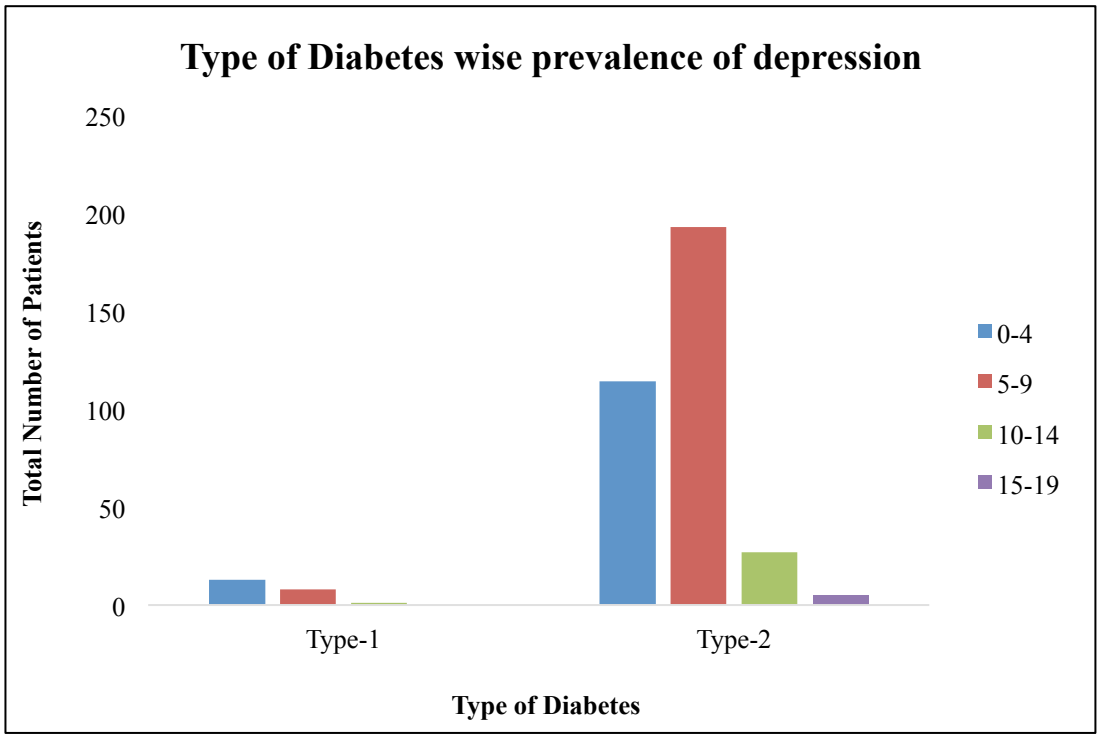


Figure 5.9 Type of diabetes wise prevalence of depression (PHQ-9)

5.6 Duration of Diabetes wise prevalence of depression:

Maximum numbers of patients were found to be having depression that was suffering from diabetes for less than ten years (N=80, 43.33 %). There were 75 (40.62 %) patients suffering from depression with the duration of diabetes of 10-20 years, and There were 30 (16.25 %) and ten patients (5.41 %) with the length of diabetes of 20-30 years and more than 30 years respectively. The study shows significant co-relation between duration of diabetes and depression.

Table 5.7 Duration of diabetes wise prevalence of depression

Duration of Diabetes	Diabetes without depression		Diabetes with depression	
	Total number of patients	Percentage (%)	Total number of patients	Percentage (%)
<10 years	130	59.58	80	43.33
10 - 20 years	29	13.29	75	40.62
20 – 30 years	3	1.37	30	16.25
>30 years	3	1.37	10	5.41

Table 5.8 Duration of diabetes wise comparison of depression

Test	Value	df	P value	Statistically Significant (P< 0.05)
Chi-square	56	3	<0.0001	Yes

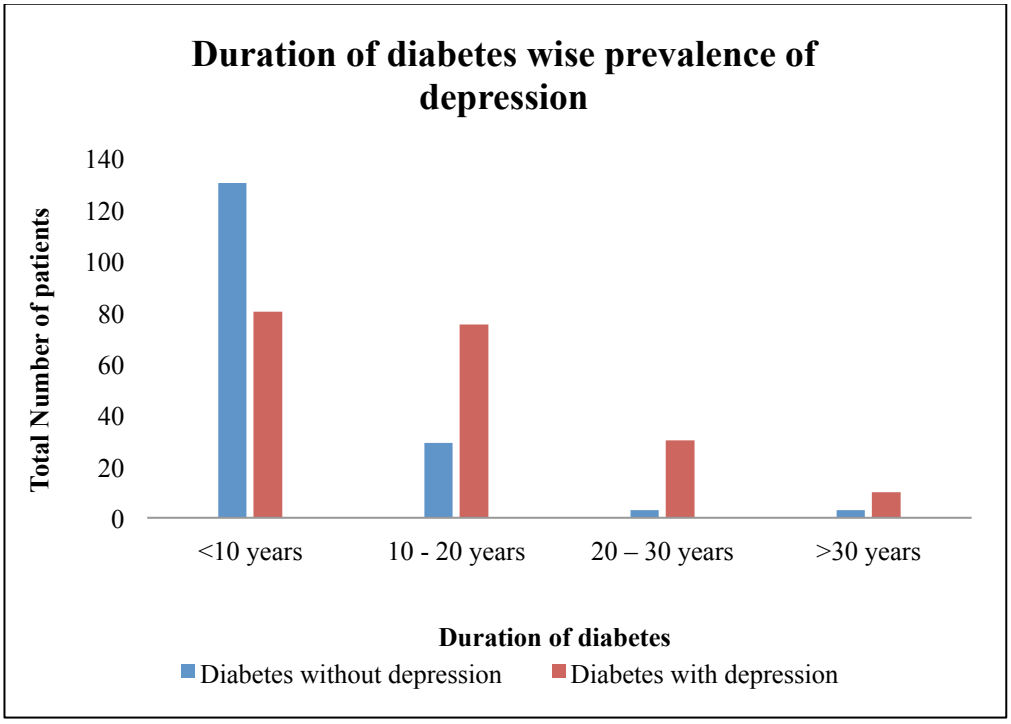


Figure 5.10 Duration of diabetes wise prevalence of depression

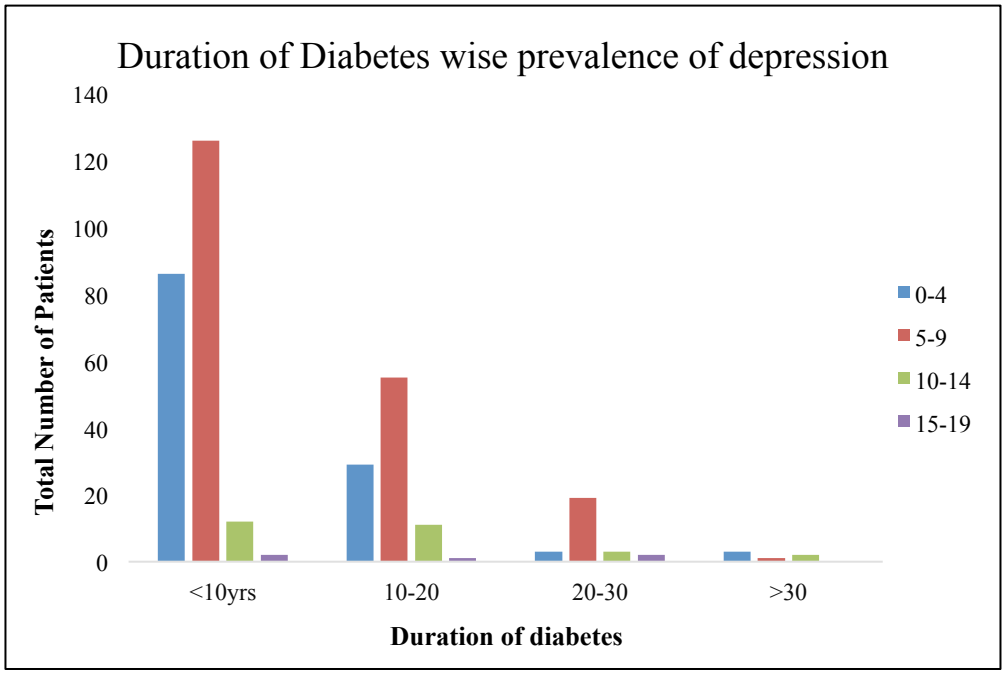


Figure 5.11 Duration of diabetes wise prevalence of depression (PHQ-9)

5.7 HbA1c wise prevalence of depression in diabetes patients:

From 361 patients, 227 (63.05%) patients with elevated HbA1c and patients with normal HbA1c (N = 6, 1.66%) level were suffering from depression. Level of HbA1c in diabetic patients with depression (8.483 ± 0.1164) was found to be slightly higher than patients without depression (8.173 ± 0.1789). But it was not statistically significant.

Table 5.9 HbA1c wise prevalence of depression

HbA1c level	Diabetes without depression		Diabetes with depression	
	Total number of patients (N)	Percentage (%)	Total number of patients (N)	Percentage (%)
Normal	8	2.22	6	1.66
Elevated	119	33.05	227	63.05

Table 5.10 HbA1c wise comparison of depression

Test	Value	df	P value	Statistically Significant (P< 0.05)
Two tailed t – test	1.505	359	0.1331	No

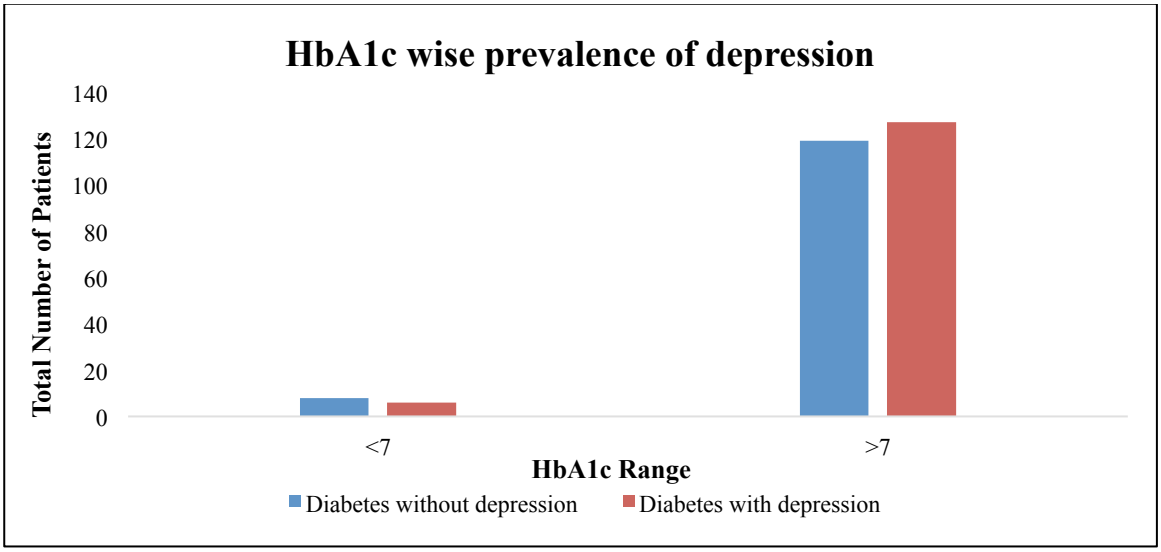


Figure 5.12 HbA1c wise prevalence of depression

5.8 Body mass index wise prevalence of depression in diabetes patients:

In the present study, the prevalence of depression was seen higher in the obese participants (61.75 %). In the underweight patients, there were equal patients (2) in both diabetes with depression and diabetes without depression. 80 (52 %) overweight patients were suffering from depression.

From the given data, there is a significant correlation found between the body mass index (BMI) and depression.

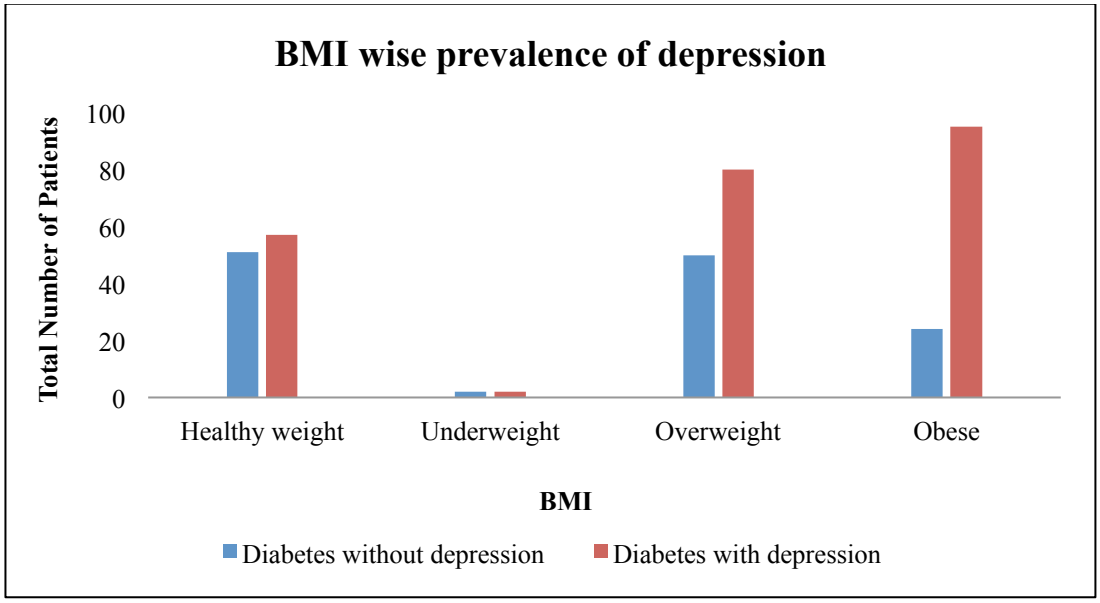
Table 5.11 BMI wise prevalence of depression

Body Mass Index (BMI)	Diabetes without Depression		Diabetes with Depression	
	Total number of patients (N)	Percentage (%)	Total number of patients (N)	Percentage (%)
Healthy Weight	51	17.99	57	37.05
Obese	24	8.86	95	61.75
Overweight	50	17.63	80	52
Underweight	2	0.70	2	1.3

***BMI: Body mass index**

Table 5.12 BMI wise comparison of depression

Test	Value	df	P value	Statistically Significant (P< 0.05)
Chi-square	19.63	3	0.0002	Yes



***BMI: Body Mass Index**

Figure 5.13 BMI wise prevalence of depression

5.9 Hypertension wise prevalence of depression in diabetes patients:

86 (20.54 %) patients with hypertension were suffering from depression and 27 (2.02 %) patients with hypertension had no signs of depression. The t-test was applied, and from present data, there was a significant correlation found between hypertension and prevalence of depression. The mean difference systolic blood pressure was 19.64 ± 1.219, and diastolic blood pressure was 13.65 ± 1.061.

Table 5.13 Hypertension wise prevalence of depression

Hypertension	Diabetes without depression		Diabetes with depression	
	Total number of patients (N)	Percentage (%)	Total number of patients (N)	Percentage (%)
	27	2.02	86	20.54

Table 5.14 Systolic blood pressure wise comparison of depression

Test	Value	df	P value	Statistically Significant (P< 0.05)
Two tailed t – test	16.11	326	<0.0001	Yes

Table 5.15 Diastolic blood pressure wise comparison of depression

Test	Value	df	P value	Statistically Significant (P< 0.05)
Two tailed t – test	12.86	274	<0.0001	Yes

5.10 Dyslipidemia wise prevalence of depression in diabetes patients:

Serum cholesterol levels were compared between diabetes without depression and diabetes with depression and the mean difference between two was 59.99 ± 4.677. It was seen as statistically significant.

Table 5.16 Dyslipidemia wise prevalence of depression

Dyslipidemia	Diabetes without depression		Diabetes with depression	
	Total number of patients (N)	Percentage (%)	Total number of patients (N)	Percentage (%)
	13	0.46	42	4.9

Table 5.17 Dyslipidemia wise comparison of depression

Test	Value	df	P value	Statistically Significant (P< 0.05)
Two tailed t – test	12.83	53	<0.0001	Yes

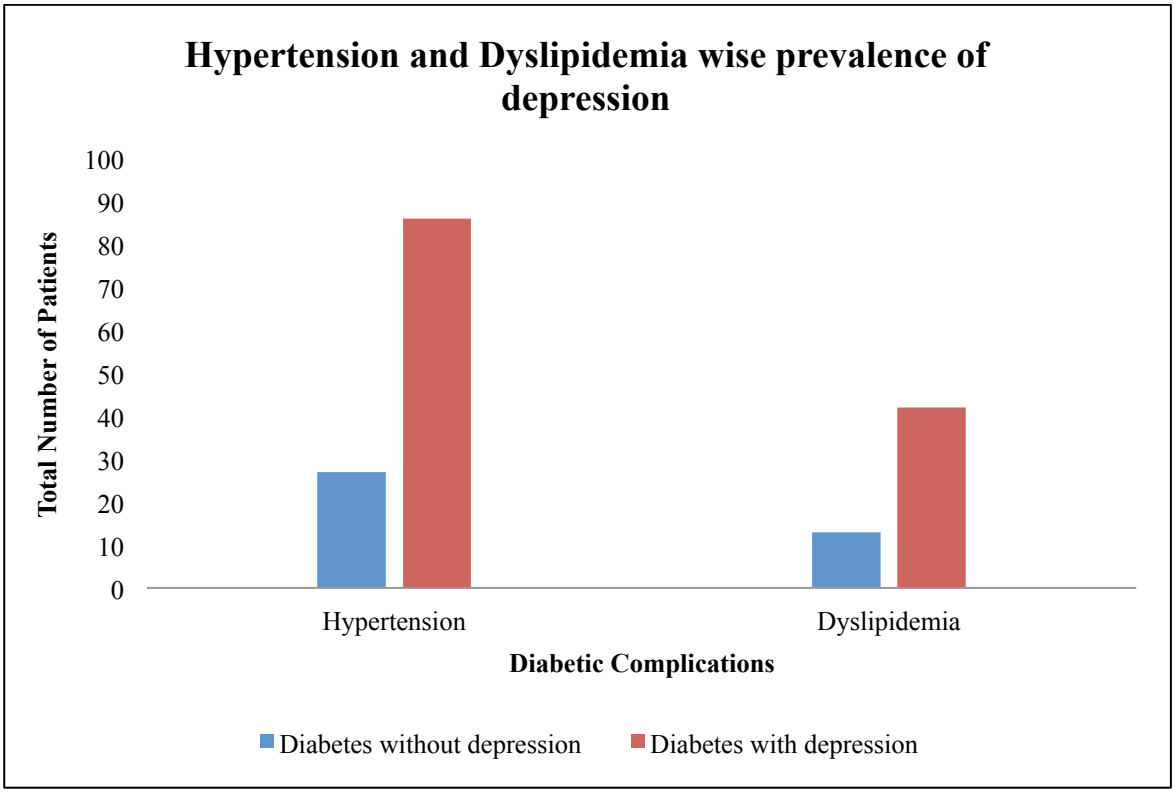


Figure 5.14 Hypertension and Dyslipidemia wise prevalence of depression

5.11 Diabetic complications wise prevalence of depression:

Patients who were suffering from depression have diabetic complication like neuropathy (N=32, 26.92 %), Retinopathy (N=8, 6.73 %), CAD (N=10, 8.41 %), Diabetic foot (N=2,

1.68 %) and Nephropathy (N=1, 0.84 %). In the present study, there was a statistically significant correlation was found between diabetic complications and depression.

Table 5.18 Diabetic complications wise prevalence of depression

Diabetic complications	Diabetes without depression		Diabetes with depression	
	Total number of patients (N)	Percentage (%)	Total number of patients (N)	Percentage (%)
Neuropathy	7	1.11	32	26.92
Retinopathy	3	0.47	8	6.73
CAD	0	0	10	8.41
Diabetic foot	0	0	2	1.68
Nephropathy	0	0	1	0.84

Table 5.19 Diabetic complications wise comparison of depression

Test	Value	df	P value	Statistically Significant (P< 0.05)
Chi – square	186.6	24	<0.0001	Yes

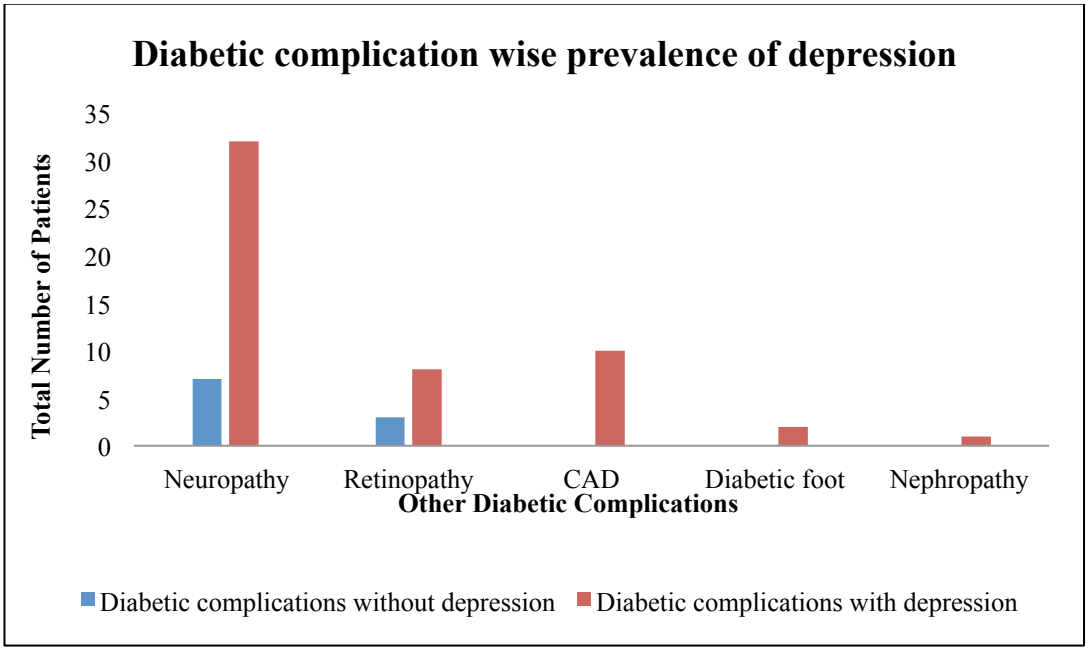


Figure 5.15 Diabetic complications wise prevalence of depression

5.12 Education wise prevalence of depression in diabetes patients:

The most substantial proportions of the participants reported with depression being HSC pass out (N = 86, 55.9 %) and immediate highest were graduates (N = 66, 42.9 %). The correlation between education level and depression was found to be statistically significant.

Table 5.20 Education wise prevalence of depression

Education	Diabetes without Depression		Diabetes with Depression	
	Total number of patients (N)	Percentage (%)	Total number of patients (N)	Percentage (%)
No Education	6	2.1	23	14.9
SSC	13	4.5	50	32.5

HSC	30	10.5	86	55.9
Graduation	63	22	66	42.9
Post-Graduation	14	4.9	9	5.8

***SSC: Secondary School Certificate, HSC: Higher Secondary Certificate**

Table 5.21 Education wise comparison of depression

Test	Value	df	P value	Statistically Significant (P< 0.05)
Chi-square	30.21	4	<0.0001	Yes

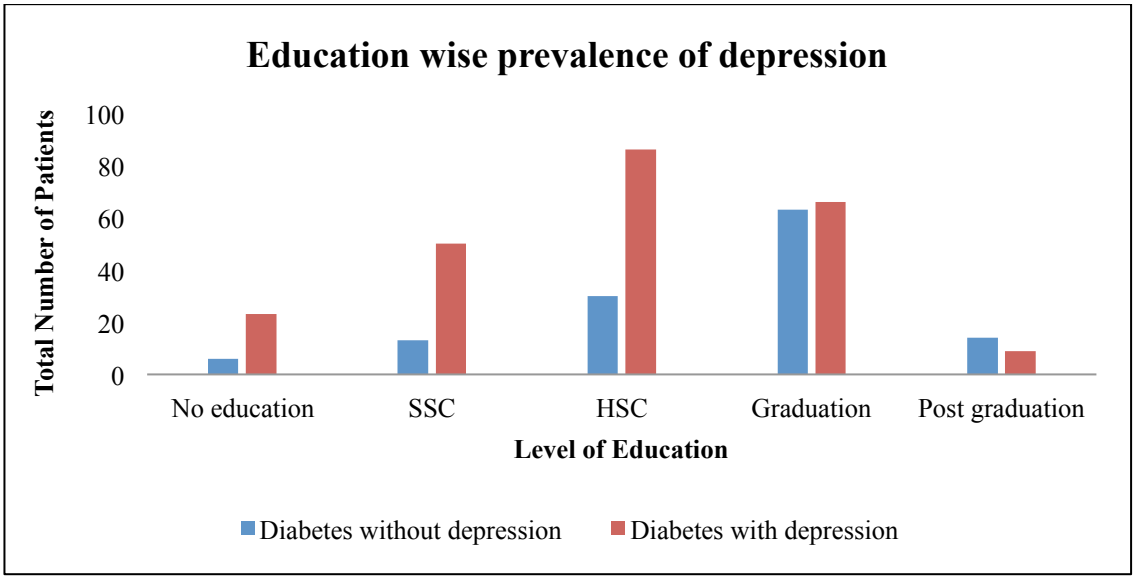


Figure 5.16 Education wise prevalence of depression

5.13 Occupation wise prevalence of depression in diabetes patients:

The prevalence of depression was seen highest in the participants who were doing household or domestic work (56.36 %) and participants who were doing the corporate job (25.33 %) and were retired (28.5 %) both were suffering from depression. From the study, the co-relation between occupation and depression was found to be statistically significant.

Table 5.22 Occupation wise prevalence of depression

Occupation	Diabetes without depression		Diabetes with depression	
	Total number of patients (N)	Percentage (%)	Total number of patients (N)	Percentage (%)
Business	22	8.06	44	27.86
Corporate	51	18.7	40	25.33
Household	22	8.06	89	56.36
Retired	16	5.86	45	28.5
Skilled manual labor	4	1.46	9	5.7
Student	17	6.23	1	0.63

Table 5.23 Occupation wise comparison of depression

Test	Value	df	P value	Statistically Significant (P< 0.05)
Chi-square	57.53	5	<0.0001	Yes

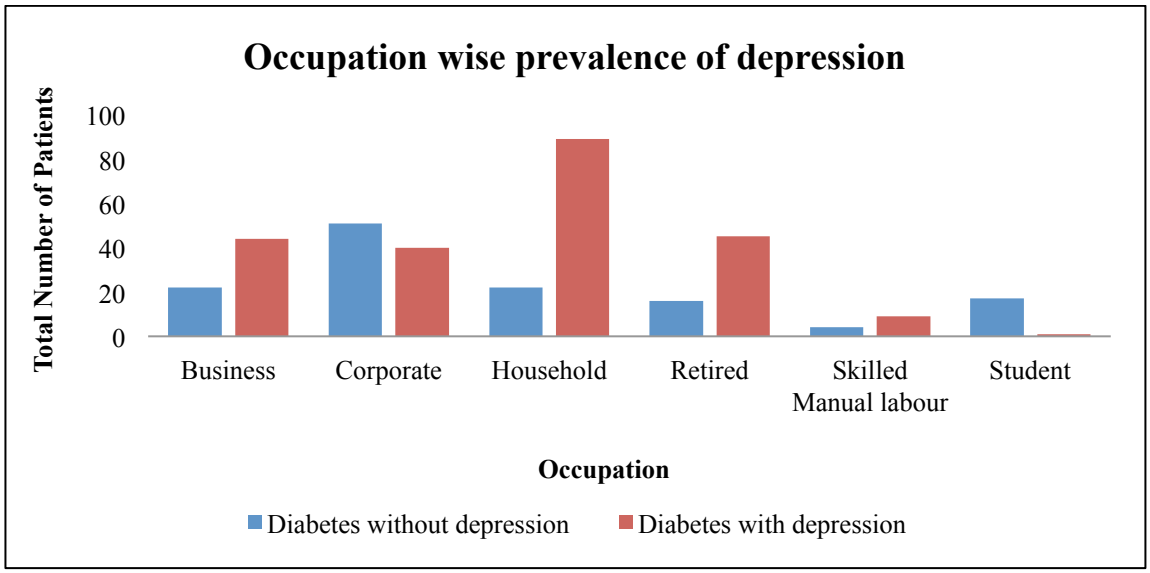


Figure 5.17 Occupation wise prevalence of depression

5.14 Marital status wise prevalence of depression in diabetes patients:

The highest number of patients found to be depressed was married (N=135, 87.37 %). The immediate highest depressed patients were widow (N= 40, 25.88%). In single patients and divorced patients depression was found 27.83 and 9.70 % respectively.

Table 5.24 Marital status wise prevalence of depression

Marital status	Diabetes without depression		Diabetes with depression	
	Total number of patients	Percentage (%)	Total number of patients	Percentage (%)
Divorced	16	5.64	15	9.70
Married	80	28.22	135	87.37
Single	19	6.70	43	27.83
Widow	12	4.23	40	25.88

Table 5.25 Marital status wise comparison of depression

Test	Value	df	P value	Statistically Significant (P< 0.05)
Chi-square	7.947	3	0.0471	Yes

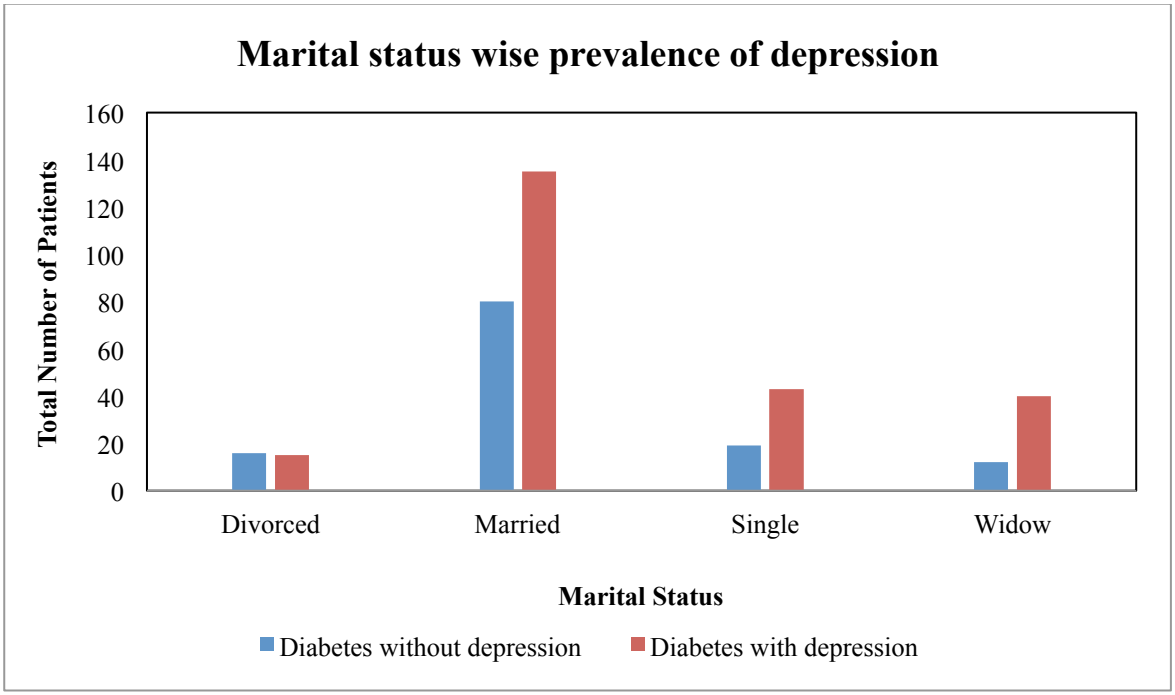


Figure 5.18 Marital status wise prevalence of depression

5.15 Physical activity wise prevalence of depression in diabetes patients:

There were 56 (32.02 %) patients who were not doing exercise daily and suffering from depression and 76 (43.48 %) patients, and 72 (41.2 %) patients were moderate and mild active respectively. From current data, there was significant co-relation seen between physical activity and depression.

Table 5.26 Physical activity wise prevalence of depression

Physical activity	Diabetes without depression		Diabetes with depression	
	Total number of patients	Percentage (%)	Total number of patients	Percentage (%)
Mild	37	15.82	72	41.2

Moderate	97	41.49	76	43.48
None	20	8.55	56	32.02

Table 5.27 Physical activity wise comparison of depression

Test	**Value**	**df**	**P value**	**Statistically Significant (P< 0.05)**
Chi-square	27.77	2	<0.0001	Yes

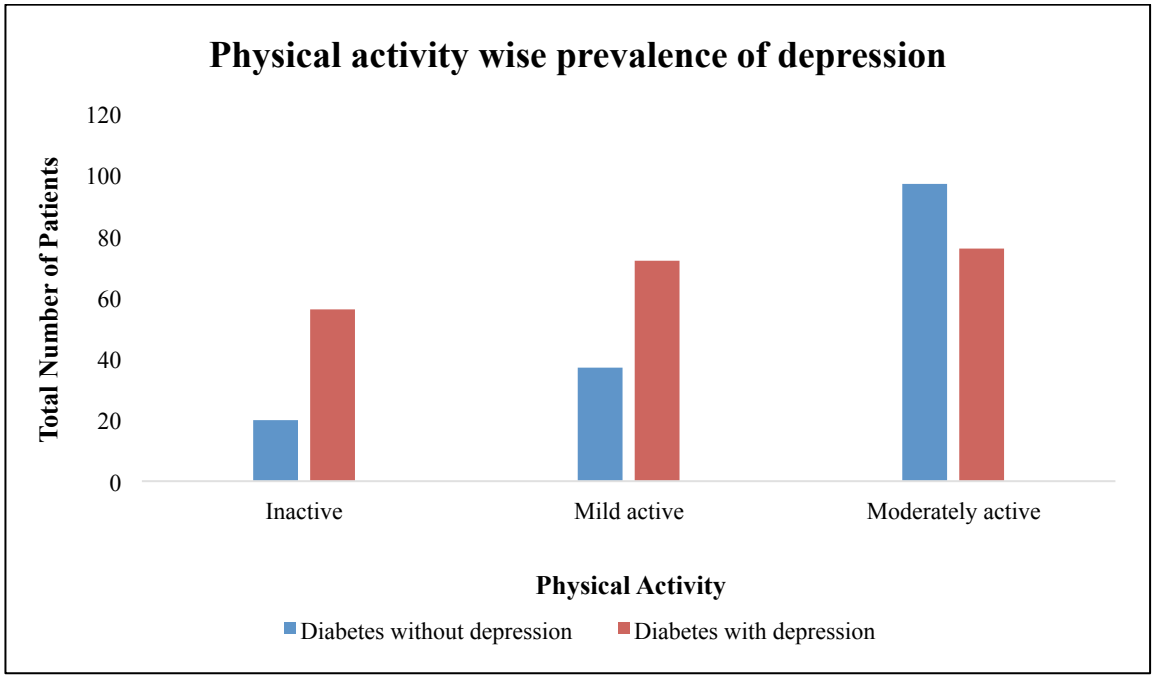


Figure 5.19 Physical activity wise prevalence of depression

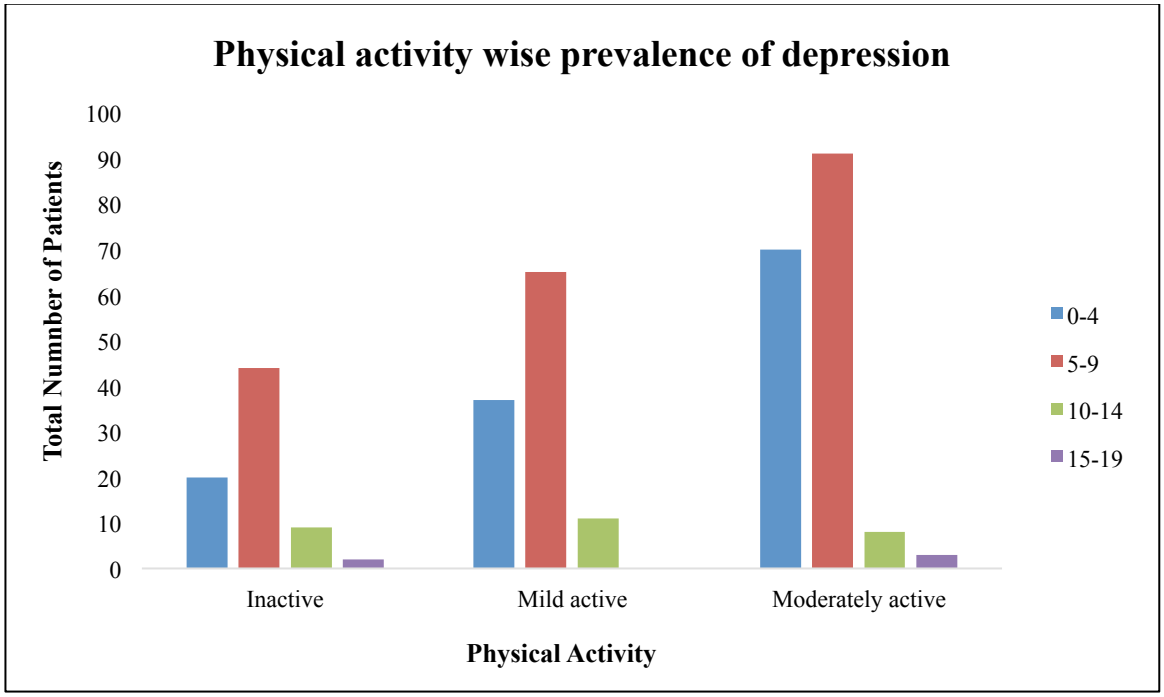


Figure 5.20 Physical activity wise prevalence of depression (PHQ-9)

5.16 Family history wise prevalence of depression in diabetes patients:

There were 90 (63.07 %) patients with the family history of diabetes was suffering from depression. The highest number of patients (N=42, 36.28%) who were not suffering from depression had family history of diabetes. 22 patients and 6 patients have family history of hypertension and CAD was not suffering from depression. The correlation between family history and depression was not statistically significant.

Table 5.28 Family history wise prevalence of depression

Family History	Diabetes without depression		Diabetes with depression	
	Total number of patients (N)	Percentage (%)	Total number of patients (N)	Percentage (%)

Diabetes	42	12.56	90	63.07
Hypertension	22	6.58	51	35.74
CAD	6	1.79	23	16.11

***CAD: Coronary Artery Disease**

Table 5.29 Family history wise comparison of depression

Test	Value	df	P value	Statistically Significant (P< 0.05)
Chi-square	1.407	2	0.4949	No

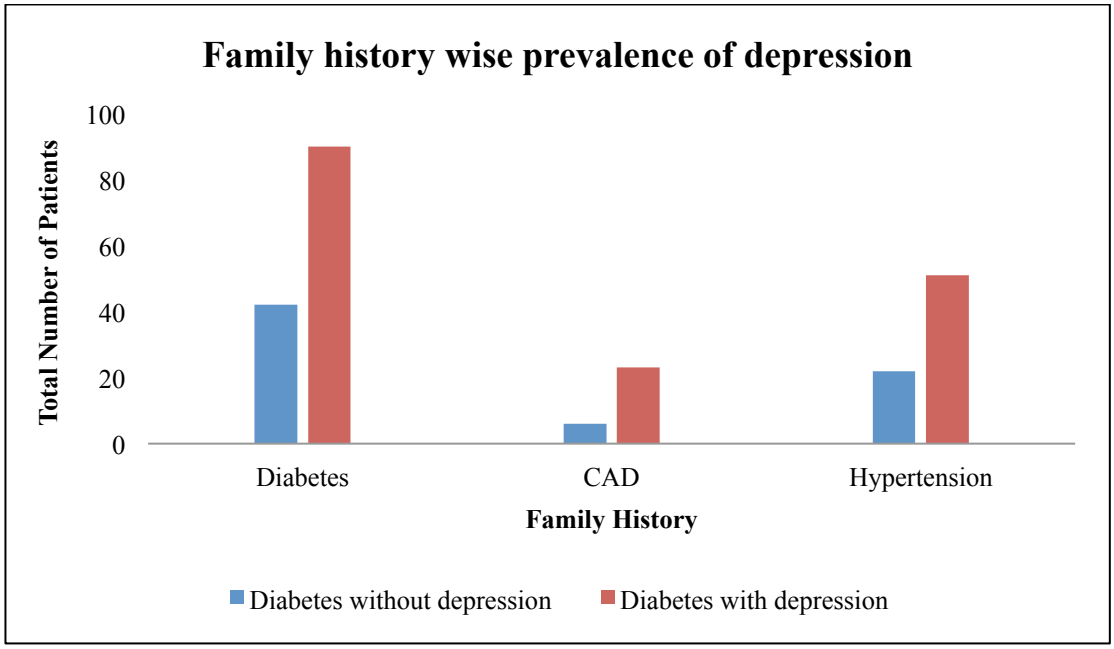


Figure 5.21 Family history wise prevalence of depression

5.17 Quality of sleep wise prevalence of depression in diabetes patients:

Out of 360 patients, we found 184 (50.96%) patients are suffering from depression, and they have disturbed sleep, which is comparatively higher than that of the non-depressive patients. There is a significant correlation seen between the quality of sleep and depression.

Table 5.30 Quality of sleep wise prevalence of depression

Quality of sleep	Diabetes without depression		Diabetes with depression	
	Total Number of patients (N)	Percentage (%)	Total number of patients (N)	Percentage (%)
Deep sleep	82	22.77	50	13.85
Disturbed sleep	44	12.18	184	50.96

Table 5.31 Quality of sleep wise comparison of depression

Test	Value	df	P value	Statistically Significant (P< 0.05)
Chi-square	70.4	3	<0.0001	Yes

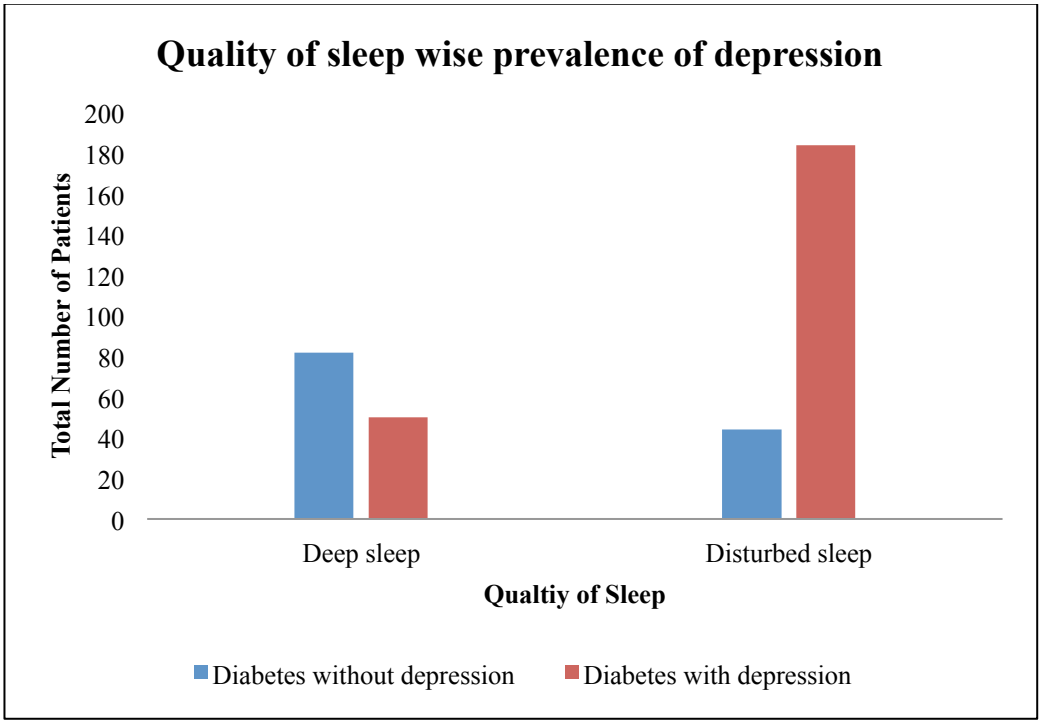


Figure 5.22 Quality of sleep wise prevalence of depression

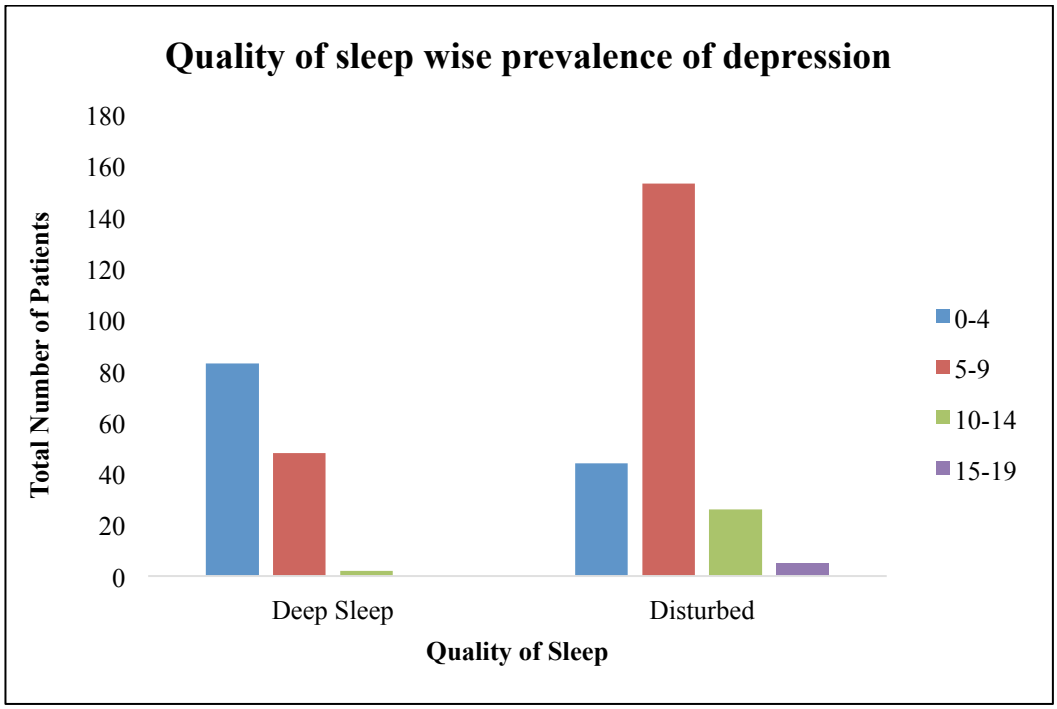


Figure 5.23 Quality of sleep wise prevalence of depression (PHQ-9)

Chapter 6

Discussion

National and state programs are implemented to create awareness and screen non-communicable diseases like diabetes, screening for depression among diabetic patients is not carried out. Diabetic patients are not aware of the fact that their mental health is also playing the significant role in the progression of their disease. The study was carried out in the diabetic patients attended the Dia – care Clinic in Ahmedabad.

The overall prevalence of any level of depression was seen in two hundred and thirty three patients (64.72 %), that was mainly mild and moderate type of depression. Only 1.38 % patients had severe depression, and 35.27% patients were diagnosed with no depressive symptoms. In one study by Katon et al. a prospective study among 2759 diabetic patients in Washington (2014) and were followed up for five years, found out that 83% of the patients were suffering from major depression as reported by Patient Health Questionnaire (PHQ - 9). The study performed in Guinea (2014) reported with the prevalence of depression of 48.3% in type – II diabetes patients. Prevalence of depression in diabetic patients was found between 30 to 83% in UK and USA (Li c et al. 2008, Kendrick et al. 2009). A study conducted by Thour et al. in Chandigarh found the prevalence of depression 41%. One study carried out in South India by Madhu et al. found the prevalence of depression 49%. In both the studies, depression was mainly associated with the reduced glycemic control. Studies carried out in Trivandrum, India found the prevalence rate of depression among patients with type – II diabetes was found to be 70%. Similar prevalence was observed in US-based independent studies (Lype et al. 2009). In another study by Raval et al. 41% of the patients were diagnosed with the depression in North India.

The changes in the prevalence among different studies suggest different environmental, cultural, ethnicity and social background, i.e., study conducted in Palestine (2014) had more depression due to stressful conditions like wars, violence, and unemployment that are major contributing factors for developing depression (Sweileh et al. 2014).

It has been recommended that diabetes (both Type – I and Type – II) can be related to the increased event of specific psychiatric issues. Self – destructive thoughts (suicidal ideas) and suicidal attempts are conceivable life-threatening emergencies that can occur more frequently in the diabetic patients than that of the general population. Numerous investigations have focused on the relationship that diabetes shares with psychological disorders, particularly depression. Association between insulin resistance and depression was studied by Mary. Insulin resistance can develop consequences of an increased release of counter regulatory hormone associated with depression (Musselman et al. 2003). Nonetheless few studies have focused upon understanding suicidal ideation among people with diabetes. In our study 3.30% among depressed participants had a suicidal thought, it is beyond the scope of this study to analyze and evaluate suicidal ideation in detail (Sarkar et al. 2014).

A few investigations have indicated relationship amongst depression and diabetes and even connect the sociodemographic characteristics were observed and related with depression.

Age is one of the major factors that is associated with diabetes and causes depression. In our study, we have found out that there is a significant correlation between age and depression in diabetic patients ($p < 0.0001$).

An investigation was done in Iran and Pakistan (2014) indicated unique relationship amongst depression and diabetic patients with age more than >50 years (Khuwaja et al. 2010, Sweileh et al. 2014). Another investigation done in Jos, Nigeria on depression among diabetic outpatients discovered 58.8% of the study populations were over the age of 40 years (Agbir et al. 2010). An investigation by Liang et al. found out an elevated amount of depressive manifestation (regardless of diabetes) among middle-aged and older Hispanics and blacks than among white Americans of a similar age group. These were all in co-ordinance with our investigations as we likewise discovered prevalence among those over 40's to be 58.72%.

In one study conducted in Illinois, USA (1992), reported that depression decreased in the middle age about 45, with the rise in the afterlife (>80 years), which is a reflection of life cycles ups and downs, related to the unemployment, marital status, and economic well being. Our study did not show any decreased level of depression above the age of 45 years, and the reason behind this might be a different culture and socio-economical status between the USA and India (Mirowsky et al. 1992). Being a developing country, chances of association between depression and lower socio-economical status is seen through the lifespan in India. Cultural differences could likewise clarify it. In India, the joint family was in vogue till recently. This gave social security to the young individuals. The separation of the joint family and rise in the nuclear family could explain the occurrence of depression in young age because of decreased family support.

In the current study, mild and severe depression was seen higher in male than female, so there was statistically significant correlation was found between the gender and depression in diabetic patients (p – 0.0213). There was one study conducted in Bangalore city among young adults who were attending college, female (18%) were found less depressed than male (25%) (Parikh et al. 2001). In contrast, several large population-based studies reported that women have higher depression than men (Blazer et al. 1994, Bebbington et al. 1998). One Meta-analysis of studies carried out in different countries demonstrated a result as women are roughly twice likely to experience or report depression in their lifespan (Nolen – Hoeksema et al. 1990).

The increased prevalence of obesity these days attracted consideration regarding the worldwide significance of this problem (Arora et al. 2012). In the USA, around two- thirds of the adult population is thought to be overweight or obese. Similar trends are being noticed worldwide (Tsai et al. 2011). Studies have shown that obese people are about 25% more likely to experience a mood disorder like depression as compared to healthy weight. Further obese patients have constantly active immune system, which contributing to chronic inflammatory state that is reported to be associated with depression (Faith et al.

2002). In our study we found significant association of obesity was found between diabetic patients with depression and without depression.

In the present study, depression is seen higher in the obese (61.75 %) and overweight patients (52 %) than the healthy weight patients, who were suffering from diabetes. Prevalence of depression is significantly correlated with the body mass index (p – 0.0002). Several studies support that depression is found higher in the obese and overweight patients and higher BMI is also a predictor for depression in Type – II diabetic patients [de Groot et al. (2007), Nichols et al. (2003), Sacco et al. (2007)].

In all the inclusive community, people with diabetes are it in type – I / type – II is prone to have depression as individuals who do not have diabetes (Ryan et al. 2001). Present study showed no significant correlation between the type – I and type – II diabetes and depression (p – 0.7058) may be the reason behind it was there were less number of patients enrolled who were suffering from type – I diabetes than type – II diabetes. In contrast one study there was a correlation found between type – I diabetes patients and depression, the majority of the patients were young adults who have a lot of dreams and wishes for their future but due to the burden of the disease they might lose hope and overcome from this situation (Khan et al. 2016). Individual patient needs counseling and education on the lifestyle modification and aware of the fact that diabetes is the chronic condition and that can be controlled without affecting routine activities.

Duration of diabetes is significantly correlated with the prevalence of diabetes-associated depression in our study ($P < 0.0001$). There was one investigation carried out in South Carolina, USA in 2014 to evaluate the independent factors related with major depressive disorder and it was identified that those patients having diabetes for at least five years were having depression. which was in consent to this study (Saydah et al. 2003). Therefore, we conclude that duration of diabetes is also one of the important contributing factors.

We did not find the significant relationship between the levels of HbA1c and depression. Only slight increase in HbA1c level was observed in diabetic patients with depression. Previous study showed that depressive symptoms were not associated with the level of HbA1c over a year period in patients with diabetes (Georgiades et al. 2007).

We found that hypertension is the significant factor and is correlated with the prevalence of depression. Rabkin et al. (1983) found that hypertension was three times more prevalent in depressive patients than non-depressive patients supporting the significant correlation between hypertension and depression.

We found the significant correlation between serum cholesterol and depression in diabetic patients ($p < 0.0001$). Many previous reported studies support this correlation. It shows significant correlation between depressive symptoms and total cholesterol and triglycerides level in cross sectional study of African American adults with type – II diabetes (Gary et al. 2000).

We have found the significant correlation between diabetic complications and depression ($p < 0.0001$). The macro – vascular and micro – vascular complications of diabetes are increased by the presence of depression in diabetes, which adds to the increased mortality rate in this population (Black et al. 2003). Another study was conducted in Chandigarh showed the higher prevalence of depression in diabetic patients and depression was strongly associated with the age, obesity, neuropathy, nephropathy, peripheral vascular disease and diabetic foot disease (Raval et al. 2010). In Chennai, study was carried out to estimate the prevalence of depression in diabetic patients, 23.4% were found depressed and significantly associated with retinopathy, nephropathy, neuropathy and peripheral vascular disease as compared to the patients without these complications (Poongothai et al. 2011).

It was evident from this investigation that subjects with comorbidities have the higher prevalence of depression this emphasizes the fact that depression should not be treated in

isolation. A holistic way is required to deal with the healthcare looking at both mental and physical wellbeing is required if we are to handle the problem of depression in the community.

In our study, we have found out that there is a significant correlation between the level of education and depression ($p < 0.0001$). Maximum numbers of patients who are suffering from depression are either completed HSC (55.9 %) or graduation (42.9 %). There was one study conducted in New Delhi, seen the prevalence of depression in type-II diabetic patients to be 27.05%. Those had depression also found out to have a low level of education (Ali et al.) Lack of education can cause low self-esteem and social isolation, which are known contributors of depression.

Depression is commonly seen in the patients with the low family income, unemployment, being dependent on others and those who are living alone or have less family support. We have seen the significant correlation in diabetic patients between occupation and prevalence of depression ($p < 0.0001$). There was one study conducted in urban Tanzania to screen common mental disorder (CMD), the prevalence of CMD was high in the unemployed than employed (Jenkins et al. 2010). For instance, the stress that outcomes from individuals losing their job and source of living could have prompted the depression development. In contrast, the presence of depression can also be the reason for the loss of job, as an individual is not anymore able to focus on the work under the presence of illness. Therefore, unemployment can be contributing factor to diabetes-associated depression.

In our study, we can postulate that marital status is significantly co-related with the prevalence of depression ($p – 0.0471$). Married (87.37 %) and single (27.83 %) people are seen profoundly depressed than that of the widow and divorced group of patients. The relationship with separation or being widow was a usual outcome as it was reported in USA (Mirowsky et al. 1992) and Finland (Salokangas et al. 1998), as separation and

divorce are well-established causes of depression. But in our study, we found more prevalence of depression in married individuals, which could be due to…

From the present study, it can be said, as physical activity is significantly correlated with the depression in diabetic patients ($p < 0.0001$). There are some results of the studies, which were conducted over time support the idea of daily physical activity had a better mental and physical health status and based on these symptoms of the mental disorders can easily be vanished (Paluska et al.). Thus, increase in physical inactivity increases likeliness of depression in diabetic patients.

In our study, the statistical significance was not found between family history and occurrence of depression. But in one study presence of positive family history of depression occurs more often in patients with depression in comparison with individuals with diabetes without depression

In our study, we can say that there was significant correlation found between the quality of sleep and depression in diabetic patients ($p < 0.0001$). Many studies revealed that depressed people experience insomnia – difficulty in sleeping or staying asleep (Robillard et al. 2014, Itani et al. 2013). Early morning awakening is a characteristic feature of depression, and it is also associated with many problems like poor deep sleep, headache, and obesity (Robillard et al. 2014, Itani et al. 2013). Thus, diabetic patients with depression are having poor quality of sleep.

Chapter 7

Conclusion

In conclusion, this study demonstrated that depression is the common comorbid condition in diabetic outpatients. Depression causes significant problems among diabetes patients. The overall prevalence of depression in diabetic patients was found to be 64.72 % with the mild, moderate and severe depression 55.56 %, 7.78% and 1.38 % respectively. 3.30% of the patients have suicidal thoughts. The present study had calculated the prevalence of depression and associated factors like Age, Gender, Body Mass Index, Physical activity, Level of education, Occupation, Hypertension, Dyslipidemia, Marital status, Quality of sleep, Duration of diabetes and Diabetic complications are significant among diabetic patients. We highly recommend the introduction of the psychological aspect of the diabetic health care plan to reduce the number of depressed or unrecognized case of depressed diabetic patients. Health care providers need to focus more on diagnosing and treating comorbid depression efficiently. This will prevent progression to more chronic or severe form of depression before its too late and to receive patient-centered service for people in real need and offer them a better quality of life.

Chapter 8

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Chapter 9

Annexures

ANNEXURE – I

AIM: Prevalence and determinants of depression in diabetic patients: An observational study in a tertiary care centre in Ahmedabad region.

INTRODUCTION

Diabetes is rising as the major concern globally as it affects every organ of our body. According to the world Health Organization (WHO) by 2025 there will be 300 million people worldwide will be suffering from diabetes. India will have highest diabetic population of 69.9 million by the 2025.

Depression is the public health concern in terms of its prevalence, economic burden, morbidity and suffering. Estimated prevalence of depression is 25% worldwide. Depressive disorders are seen more in women than men. In total lifespan of human there are 10-20% chances of suffering from depression.

Depression is common among people with diabetes, and it is associated with worse diabetes outcomes. The prevalence of depression is higher in patients with diabetes who have long-term complications. Compared with patients with diabetes alone, patients with depression and diabetes have been shown to have poorer self-management and poor adherence to antidiabetic, lipid-lowering and antihypertensive treatment. Depression may be an important barrier to effective diabetes management. Patients with depression and diabetes are more likely to have higher macrovascular and microvascular complications and higher mortality rates.

Depression is more likely to be seen in long-term diabetic patients. They are more likely to have risk factors like sedentary life style, obesity, alcohol consumption, smoking and uncontrolled hyperglycemia

The data regarding prevalence study is not available enough in India. We will investigate the prevalence and determinants of depression in Diabetic patients who attend tertiary care hospital in Ahmedabad region and its association with glycemic control, diabetic complication, demographic and socioeconomic factors.

MATERIAL AND METHOD

Study Design

This will be an observational single centric study and will have prospective component.

All consecutive patients with diabetes attending Hospital will be evaluated. Informed and written consent will be obtained from all the participants. Patients with established diabetes will be examined consecutively for depression by PHQ-9 (a subset of the Patients Health Questionnaire). Further, Social, demographical and clinical variables will be also assessed.

Study Population and Sample size:

For the quantitative component of the study, the study population consists of new or already registered patients with diabetes attending tertiary diabetes center during a 4‐month period from January to April 2018.

For the qualitative component of the study, patients with diabetes will be assessed for depression by using the nine-item PHQ-9 in one‐on‐one interviews.

Sample size: 360 patients

Inclusion Criteria:

1. A diagnosed case of diabetes.
2. Patient age >18 years
3. Duration of diabetes >1 year.

4. Subjects who were willing to participate in the study

Exclusion Criteria:

1. Patient age <18 years
2. A patient who is not willing to sign the consent form
3. A patient who doesn't understand the questionnaires or deaf or not able to answer is excluded.

EVALUATION PARAMETERS:

Age group in years	18-80
Gender	Male Female
Education	None Primary Secondary Undergraduate Postgraduate
Occupation	Professional/Corporation Medium business Skilled manual labor Household/Domestic Unemployed/Retired Other
Marital status	Single Married Widower Divorced
Physical activity	Mild Moderate None
Body mass index (kg/m2)	Underweight - <18.5 Healthy Weight - 18.5 – 24.9 Overweight - 25–29.9

	Obese - ≥30
Serum cholesterol (mg/dl)	Normal - <200 High - ≥200
Glycated Hemoglobin (%)	Normal - ≤ 7 High - >7
Blood pressure	Systolic blood pressure <120mmHg Diastolic blood pressure <80mmHg
Micro vascular complications	Neuropathy Nephropathy Retinopathy
Macro vascular complications	Coronary artery disease Peripheral vascular disease Stroke Diabetic foot

ANNEXURE – II

Case report form for Diabetic Patient

Title of study: Prevalence and determinants of depression in diabetic patients: An observational study in a tertiary care centre in Ahmedabad region.

Name of Principal Investigator: Ms. Kavisha Raval

Name of Organization: Institute of Pharmacy, Nirma University

Name of the Guide: Dr. Snehal Patel

Designation of the guide: Assistant Professor at Institute of Pharmacy, Nirma University

Study Site (Hospital): Dia care Clinic, Gandhipark, Near Nehrunagar Circle, Ahmedabad, Gujarat, India

1. **Personal Details:**

Age:	**Height:**
Gender:	**Weight:**
City:	**State:**

A) Body Mass Index (kg/m2)

Underweight	☐	**<18.5**
Healthy Weight	☐	**18.5 – 24.9**
Overweight	☐	**25 – 29.9**
Obese	☐	**≥30**

Education		**Occupation**	
No education	☐	Professional/Corporation	☐

S.S.C	☐	Medium business	☐
H.S.C	☐	Skilled manual labor	☐
Graduation	☐	Household/Domestic	☐
Higher education	☐	Unemployed/Retired	☐
		Other	☐

B) Marital Status:

Single	
Married	
Widow	
Divorced	

C) Physical Activity:

Mild	
Moderate	
None	

2. Medical History:

Family history of any of the following disorders?

Cardiovascular disorders		**Obesity**	
Hypertension		Diabetes	

Are you currently taking any medications? If so, please list them, their doses and your reason for taking them.

_____

___

_____

___

_____

___

3. Diet

Are you vegetarian? ☐ Or non-vegetarian ☐ or Consuming Eggs ☐

4. Environmental effects and behaviour ☐

Quality of sleep: Deep sleep ☐ Sleep with disturbances
Quantity of sleep (Hours): _____

5. **Biochemistry Profile:**

Serum cholesterol (mg/dl)		**Normal**	
		High	
Glycated Hemoglobin (%)		**Normal**	
		High	

6. **Blood Pressure Measurement:**

Systolic Blood Pressure (mmHg)		**Normal**	
		Elevated	
		Stage 1 Hypertension	
Diastolic Blood Pressure (mmHg)		**Stage 2 Hypertension**	

7. **Diabetic Complications:**

Microvascular Complications	**Neuropathy**	
	Nephropathy	
	Retinopathy	
Macrovascular Complications	**Coronary artery disease**	
	Peripheral vascular disease	
	Stroke	
	Diabetic foot	

DATE: _____

ANNEXURE – III

Informed Consent Form

Informed Consent Form for the patients, who would be attended by the investigator and would be asked to participate in the study of "Prevalence of depression in diabetic patients"

Name of Principal Investigator: Ms. Kavisha Raval

Name of Organization: Institute of Pharmacy, Nirma University

Name of the Guide: Dr. Snehal Patel

Designation of the guide: Assistant Professor at Institute of Pharmacy, Nirma University

Name of Proposal and version: Prevalence and determinants of depression in diabetic patients: An observational study in a tertiary care centre in Ahmedabad region.

PART I: Information Sheet

Introduction:

I, Ms. Kavisha Raval studying at Institute of Pharmacy, Nirma University am doing research on "Prevalence of depression in diabetic patients: A cross sectional study in a tertiary care center in Ahmedabad region." under the guidance of Dr. Snehal Patel. We wish to invite you as a patient to participate in this research.

Purpose:

Depression may contribute to poor diabetes- related outcomes, diabetes and its complications may also contribute to poor depression outcomes. The available data

regarding the prevalence of depression in diabetes patients in India are limited. Therefore, objective of study is to investigate prevelance of depression in diabetic patients is required.

Type of Research Intervention:

I will ask you some question for your routine; socio-economic activity and status, BMI, height, weight, gender, age, diet, occupation, medical history of some diseases and symptoms related to depressive disorders etc. that will help to find out the presence and progression of depression.

Participant selection:

Patients with the known history of diabetes are being enrolled for the study.

Procedures and Protocol:

Firstly, the investigator will come to fill up the Questionnaire from the patients. All the questions will be answered by patients. The answers will be kept confidential. After that, final evaluation will be done from the Statistical Data.

Risks:

There are no risks involved in this research.

Benefits:

This study is important for finding the Prevalence of depression in diabetic patients.

Reimbursements:

You will not be provided any incentive to take part in this research.

Confidentiality:

The information that we collect from this research project will be kept confidential. Information about the patients that will be collected from the research will be put away and no-one but the researchers will be able to see it..

Sharing of the results:

Confidential information will not be shared.

Right to Refuse or Withdraw:

If any of the subjects feels that they are not comfortable to fill the questionnaire regarding this research or he/she cannot give the information regarding this research, they are free to withdraw from the research.

Whom to Contact:

If you have any questions you may ask them now or later, even after the study has started. If you wish to ask questions later, you may contact: Ms. Kavisha Raval, PG Student, Institute of Pharmacy, Nirma University, Mobile No: 9925902910, E-mail: 16mph704@nirmauni.ac.in]

PART II: Certificate of Consent

Name of Participant: _____

Address of the participant: _____

Date: _____ (Day/month/year)

Statement by the person taking part in the study

I have accurately read out the information sheet provided by the investigator and understand that the following will be done:

1. Checking for the height, weight and BMI etc.
2. Socio-economic evaluation.
3. Medical history evaluation.
4. The data will be kept confidential.
5. I confirm that I was given the opportunity to ask questions about the study, and all the questions asked by me have been answered correctly.
6. I confirm that I have not been forced to give consent, and the consent has been given freely and voluntarily.

Name of the Participant: _____

Signature of the participant: _____

Date: _____ (Day / Month/ Year)

ANNEXURE – IV

જાણકાર સંમતિ પત્ર

દર્દીઓ માટે જાણકાર સંમતિ પત્ર - જે તપાસનીશ દ્વારા રજુ કરવામા આવશે અને અભ્યાસમાં ભાગ લેવા માટે કહેવામાં આવશે.

મુખ્ય તપાસનીશનું નામ: કુ. કવિશા રાવલ
સંસ્થાનું નામ: ઇન્સ્ટિટ્યૂટ ઓફ ફાર્મસી, નિરમા યુનિવર્સિટી.

માર્ગદર્શિકાનું નામ: ડૉ. સ્નેહલ પટેલ
માર્ગદર્શિકાના હોદ્દો: સહાયક પ્રોફેસર
ઇન્સ્ટિટ્યૂટ ઓફ ફાર્મસી, નિરમા યુનિવર્સિટી.

પ્રસ્તાવ: ડાયાબિટીક દર્દીઓમાં ડિપ્રેશનનું પ્રમાણ: અમદાવાદ પ્રદેશમાં તૃતીય સંભાળ કેન્દ્ર માં ક્રોસ વિભાગીય અભ્યાસ.

આ જાણકાર સંમતિ ફોર્મમાં બે ભાગ છે:
- **માહિતી પત્ર**
- **સંમતિનું પ્રમાણપત્ર**

ભાગ I: માહિતી પત્ર

પ્રસ્તાવના
હું કુ. કવિશા રાવલ, નિરમા યુનિવર્સિટી ખાતે ક્લિનિકલ ફાર્મસીમાં અભ્યાસ કરુ છું. ડૉ. સ્નેહલ પટેલના માર્ગદર્શન હેઠળ, અમે "ડાયાબિટીક દર્દીઓમાં ડિપ્રેશનનું પ્રમાણ: અમદાવાદ પ્રદેશમાં તૃતીય સંભાળ કેન્દ્ર માં ક્રોસ વિભાગીય અભ્યાસ." વિષય પર અભ્યાસ કરી રહ્યા છે. આ જ હેતુ સાથે, અમે આ અભ્યાસમાં ભાગ લેવા તેમજ યોગદાન આપવા માટે દર્દી તરીકે તમને આવકારીએ છીએ.

ઉદ્દેશ
ડાયાબિટીસ આ દેશમાં સૌથી સામાન્ય રોગ છે પણ તેની વધતી જતિ જટિલતાઓ લોકોને માનસીક ડિપ્રેશન તરફ દોરી શકે છે. આવા સંજોગો અંગે ઉપલબ્ધ માહિતી ખૂબ જ મર્યાદિત છે. તેથી, આ અભ્યાસનો ઉદ્દેશ ડાયાબિટીક દર્દીઓમાં ડિપ્રેશનના વધતા જતા પ્રમાણ અંગે વધુ માહિતી એકત્ર કરવાનો છે.

અભ્યાસનો પ્રકાર
હું તમને કેટલાક નિત્યક્રમ, સામાજિક-આર્થિક પ્રવૃતિ અને સ્થિતિ, ઊંચાઈ, વજન, લિંગ, ઉંમર, આહાર, વ્યવસાય, તબીબી ઇતિહાસ, ડિપ્રેસિવ ડિસઓર્ડર સંબંધિત લક્ષણો વગેરે વિશે પ્રશ્નો પૂછીશ, જે ડિપ્રેશન હાજરી અને/અથવા તેનુ વધતુ જતુ પ્રમાણ શોધવા માટે મદદ કરશે.

સહભાગીઓની પસંદગી
અભ્યાસ માટે ડાયાબિટીસ ધરાવતા દર્દીઓની નોંધણી કરવામાં આવી રહી છે.

કાર્યપ્રણાલી અને પ્રોટોકોલ
દરેક દર્દી પ્રશ્નાવલિ ભરવા માટે તપાસકર્તા પાસે જશે. બધા પ્રશ્નોના જવાબ દર્દીઓ દ્વારા ખુદ આપવામા આવશે. જવાબો ગોપનીય રહેશે. તે પછી, આંકડાકીય માહિતીના આધારે અંતિમ મૂલ્યાંકન કરવામાં આવશે.

જોખમો
આ અભ્યાસમાં કોઈ જોખમ સામેલ નથી.

ફાયદા
જો દર્દી આ અભ્યાસમાં ભાગ લે છે, તો તે / તેણી તેમના માનસિક સ્વાસ્થ્યની સ્થિતિ જાણવા મળી શકે છે. દર્દી માટે કોઇ અન્ય લાભ હોઇ શકતો નથી, પરંતુ અભ્યાસમાં તેમનુ યોગદાન મહત્વપૂર્ણ રહેશે. અભ્યાસના આ તબક્કે સમાજને કોઇ ફાયદા ન પણ હોઇ શકે, પરંતુ ભવિષ્યની પેઢીઓને હાલના આંકડાકીય માહિતીથી ફાયદો થવાની શક્યતા છે.

ભરપાઇ ખર્ચ
તમને આ અભ્યાસમાં ભાગ લેવા માટે કોઇ ભરપાઇ ખર્ચ આપવામાં આવશે નહીં.

ગોપનીયતા
અમે આ પ્રોજેક્ટમાંથી જે માહિતી એકત્રિત કરીએ છીએ તે ખાનગી રાખવામાં આવશે. દર્દીઓ વિશેની માહિતી મુખ્ય તપાસનીશ અથવા પ્રોજેક્ટ માર્ગદર્શિકા સિવાય કોઇપણને સાથે અથવા આપવામાં નહીં આવે.

પરિણામની શેરિંગ
ગોપનીય માહિતી શેર કરવામાં આવશે નહીં.

ઇનકાર કરવાનો અથવા નિર્ણય પાછો લેવાનો અધિકાર
આ એક પુષ્ટિકરણ છે કે દરેક દર્દીની ભાગીદારી સ્વૈચ્છિક છે અને તમને નિર્ણય પાછી ખેંચવાનો અધિકાર છે. જો કોઇ દર્દીને લાગે કે આ અભ્યાસ સંબંધિત પ્રશ્નાવલિ ભરવા માટે તેઓ આરામદાયક નથી અથવા તે આ અભ્યાસ સંબંધિત માહિતી આપી શકતા નથી, તો તેઓ અભ્યાસમાંથી પોતાનુ નામ પાછુ ખેંચી શકે છે.

કોનો સંપર્ક કરવો
જો તમારી પાસે કોઇ પ્રશ્નો હોય તો તમે હવે અથવા પછીથી નીચે રજૂ કરેલ વ્યક્તિ સાથે સંપર્ક કરી શકો છો:

કુ. કવિશા રાવલ
પી.જી. વિદ્યાર્થી (એમ. ફોર્મ.)
ઇન્સ્ટિટ્યૂટ ઓફ ફાર્મસી, નિરમા યુનિવર્સિટી.

મોબાઇલ: 9925902910
ઇ-મેઇલ: 16mph704@nirmauni.ac.in

ભાગ II: સંમતિનું પ્રમાણપત્ર

સહભાગીનું નામ: _____
સહભાગીનું સરનામું: _____
તારીખ: _____ (દિવસ / મહિનો / વર્ષ)

અભ્યાસમાં ભાગ લેતા વ્યક્તિ દ્વારા નિવેદન
હું તપાસકર્તા દ્વારા પૂરી પાડવામાં આવેલ માહિતી શીટને યોક્કસપણે વાંચી ચુકેલ છું અને સમજું છું. જે નીચે મુજબ કરવામાં આવશે:

1. ઊંચાઇ, વજન અને બીએમઆઇ વગેરે માટે ચકાસણી.
2. સામાજિક-આર્થિક મૂલ્યાંકન
3. તબીબી ઇતિહાસનું મૂલ્યાંકન
4. ડેટા ગુપ્ત રાખવામાં આવશે.
5. હું પુષ્ટિ કરું છું કે મને અભ્યાસ વિશે પ્રશ્નો પૂછવાની તક આપવામાં આવી હતી અને મારા દ્વારા પૂછવામાં આવેલા બધા પ્રશ્નોને યોગ્ય રીતે જવાબ આપવામાં આવ્યો છે.
6. હું પુષ્ટિ કરું છું કે મને સંમતિ આપવા માટે ફરજ પાડવામાં આવી નથી અને સંમતિ મુક્તપણે અને સ્વેચ્છાએ આપવામાં આવી છે.

સહભાગીનું નામ: _____

સહભાગીની હસ્તાક્ષર: _____

તારીખ: _____ (દિવસ / મહિનો / વર્ષ).

ANNEXURE – V

PATIENT HEALTH QUESTIONNAIRE-9 (PHQ-9)

Over the last 2 weeks, how often have you been bothered by any of the following problems? *(Use "✔" to indicate your answer)*	Not at all	Several days	More than half the days	Nearly every day
1. Little interest or pleasure in doing things	0	1	2	3
2. Feeling down, depressed, or hopeless	0	1	2	3
3. Trouble falling or staying asleep, or sleeping too much	0	1	2	3
4. Feeling tired or having little energy	0	1	2	3
5. Poor appetite or overeating	0	1	2	3
6. Feeling bad about yourself — or that you are a failure or have let yourself or your family down	0	1	2	3
7. Trouble concentrating on things, such as reading the newspaper or watching television	0	1	2	3
8. Moving or speaking so slowly that other people could have noticed? Or the opposite — being so fidgety or restless that you have been moving around a lot more than usual	0	1	2	3
9. Thoughts that you would be better off dead or of hurting yourself in some way	0	1	2	3

FOR OFFICE CODING 0 + _____ + _____ + _____

=Total Score: _____

If you checked off any problems, how difficult have these problems made it for you to do your work, take care of things at home, or get along with other people?

Not difficult at all	Somewhat difficult	Very difficult	Extremely difficult
☐	☐	☐	☐

Developed by Drs. Robert L. Spitzer, Janet B.W. Williams, Kurt Kroenke and colleagues, with an educational grant from Pfizer Inc. No permission required to reproduce, translate, display or distribute.

ANNEXURE – VI

દરદીના સ્વાસ્થ્યને લગતી ટૂંકી પ્રશ્નાવલી

Gujarati

આ પ્રશ્નાવલી તમને શક્ય એટલી સારામાં સારી સારવાર આપવા માટેનો એક અગત્યનો ભાગ છે. તમારા જવાબના આધારે તમારી સમસ્યાઓ સમજી શકાશે. મહેરબાની કરીને, દરેક સવાલનો શક્ય એટલો સચોટ જવાબ આપો. સિવાય કે તમને કોઈ સવાલ છોડી દેવાની વિનંતી કરવામાં આવે.

દરદીનું ટૂંકું નામ _____ ઉંમર _____ લિંગ : ☐ સ્ત્રી ☐ પુરુષ આજની તારીખ _____

છેલ્લાં ૨ અઠવાડિયામાં, તમને નીચેની કોઈ પણ સમસ્યાનો કેટલી વાર અનુભવ થયો છે ?

	જરાય નહીં	ઘણી વાર	અડધાથી વધારે દિવસોમાં	લગભગ રોજ
પ્રવૃત્તિ કરવામાં ઓછો રસ અથવા ઓછો આનંદ	☐	☐	☐	☐
હતાશા, ઉદાસી અથવા નિરાશા લાગવાં	☐	☐	☐	☐
ઊંઘ મોડી આવવી, વચ્ચે ઊંઘ ઊડી જવી, વધારે ઊંઘ આવવી	☐	☐	☐	☐
થાક અથવા અશક્તિ	☐	☐	☐	☐
ભૂખ ઓછી લાગવી કે વધારે લાગવી	☐	☐	☐	☐
તમને તમારા વિશે ખરાબ લાગે અથવા તમે નિષ્ફળ ગયા છો અથવા તમે તમારી અથવા તમારાં સ્વજનોની અપેક્ષા સંતોષી નથી એવી લાગણી થાય	☐	☐	☐	☐
છાપાં વાંચવા કે ટીવી જોવા જેવી બાબતોમાં એકધ્યાન રહેવામાં તકલીફ	☐	☐	☐	☐
હલનચલન અથવા બોલવાનું એટલું ધીમું હોય કે બીજા લોકોનું ધ્યાન જાય. અથવા એનાથી ઊલટું, એટલો બધો રઘવાટ અથવા અસ્વસ્થતા કે તમે રાબેતા કરતાં વધારે ઝડપથી આમતેમ ફરતા હતા	☐	☐	☐	☐
મરવાનો અથવા તમને પોતાને કોઈક રીતે ઈજા કરવાનો વિચાર આવે	☐	☐	☐	☐

ANNEXURE – VII

Institutional Ethical Committee, Nirma University

Item No.:3
Project No.: IEC/NU/18/IP/03

CERTIFICATE

This is to certify that the Project entitled "**Prevalence of depression in diabetic patients: A cross sectional study in a tertiary care centre in Ahmedabad region** " submitted by Dr. Snehal Patel, Institute of Pharmacy, Nirma University Ahmedabad, has been approved by the IEC, Nirma University.

Name of the Member Secretary

Dr. Sriram Seshadri
Member Secretary

27th February, 2018
Signature with Date

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