Comparison of Artificial Neural Network and Logistic Regression Models for

Prediction of Diabetes Type II with Complications

By

Muteb Hamed Saleh Alshammari

A Dissertation Submitted to

Rutgers, The State University of New Jersey

Rutgers Biomedical and Health Sciences

School of Health Related Professions

In partial fulfillment of the Requirements

For the Degree of

Doctoral of Philosophy

June 14, 2016

Final Dissertation Approval Form

Comparison of Artificial Neural Network and Logistic Regression Models for Prediction

of Diabetes Type II with Complications

BY
Muteb Hamed Saleh Alshammari

Dissertation Committee:

Frederick Coffman PhD, Committee Chair

Syed Haque PhD, Committee Member

Shankar Srinivasan PhD, Committee Member

Approved by the Dissertation Committee:

_____   Date _____

_____   Date _____

_____   Date _____

_____   Date _____

_____   Date _____

_____   Date _____

ABSTRACT

Type II diabetes mellitus (T2DM) is a growing health concern in the United States, affecting almost 30 million individuals, and currently ranking as the 7th leading cause of mortality. In addition, T2DM is associated with multi-systemic complications that contribute to both early mortality and decreased quality of life. Individuals with T2DM can be diagnosed by blood glucose tests, and previous studies have demonstrated increased risk factors for T2DM development, including obesity, particular ethnicities, personal history of polycystic ovary disease, or a family history of T2DM.

The present study aimed to find the connection between T2DM complications including ketoacidosis, hyperosmolarity, renal manifestations, ophthalmic manifestations, neurological manifestations, and peripheral circulatory diseases with the most widespread risk factors, including gender, race, family history of diabetes, obesity, smoking, alcohol-related disorders, hyperlipidemia, hypertension, hypercholesterolemia, asthma, Vitamin D deficiency, and age. The strongest association was found between increasing age and peripheral circulatory disorders, with those over 65 years showing the highest correlation (OR=22.081). Strong connections were also found between Asian/Pacific Islanders and age >65 with renal complications, as well as between alcohol abuse and hyperglyceridemia with ketoacidosis (OR=3.303 and 2.992 respectively).

This study also tested two predictive models, Logistic Regression and Neural Network (ANN), in modeling T2DM with complications. Classification methods tests showed that three complications – renal manifestations, neurological manifestations, and

ketoacidosis – were better predicted by these models than the other complications, and that both models performed very similarly in both sensitivity and specificity. This study demonstrates that specific combinations of risk factors can predict increased probabilities of specific complications in T2DM patients, and that a neural network analysis model can predict these relationships as accurately and with the same sensitivity as a standard linear regression model.

ACKNOWLEDGMENTS

Firstly, I would like to express my sincere gratitude to my advisor Prof. Frederick Coffman for the continuous support of my Ph.D. study and related research. I am very thankful to him for his endless support.

I would like to thank the members of my committee Prof. Syed Haque, Prof. Shankar Srinivasan and Prof. Masayuki Shibata for their useful comments and encouragement.

My sincere thanks also goes to all faculty and stuff of Department of Health Informatics for their kindness and support.

Last but not the least, I would like to thank my family: my parents and to my brothers and sisters for supporting me spiritually throughout my study.

TABLE OF CONTENTS

LIST OF FIGURES

LIST OF TABLES

CHAPTER I

INTRODUCTION

Among the numerous causes of mortality and morbidity across the world is diabetes type 2. Both types of diabetes (type 1 & 2), remain to be the 7th leading causes of death in the US. In 2010, more than 69, 071 death certificates were issued; a condition that pointed that diabetes was an underlying cause of death. A total of 234, 051 deaths also depicted that diabetes was both a contributing and an underlying cause of death in the US [6]. People who have been diagnosed with diabetes experience sugar levels that are higher than normal. The body develops resistance to insulin, with the pancreas producing extra insulin to cover up for the deficiency. In this, the normal blood glucose cannot be produced.

Diabetes type 2 is a common illness which is largely preventable. Of all the diabetes type 2 cases, this illness accounts for 90 to 95% of the adults. The current statistics have depicted that 29.1 million people in the US have diabetes. However, a number of these people have been diagnosed with the illness, while others are unaware of their condition. Since 2012, the prevalence of diabetes type 2 was noted to be on the rise [6].

A blood test is required to reflect the average blood sugar for a period of not more than three months. This is known as the glycated hemoglobin (AIC) test. The test is used to measure the amount of sugar that is attached to the oxygen-carrying protein (hemoglobin) in red blood cells. If more sugar is attached to hemoglobin, then, it means

that the blood sugar levels are high. Many experts have opted for this kind of test in efforts to establish whether a patient is suffering from Prediabetes or diabetes type 2. This research demonstrates successful and innovative applications of artificial neural networks in efforts to diagnose health problems. The current increasing concern that T2DM attracts is attributed to the serious consequences caused by both the disease itself and its associated multi-systemic complications. The chronic complications associated with T2DM not only trigger escalating burden to the national health systems and heighten the rate of diabetes-associated morbidity, but also lead to untimely mortality and reduced quality of life [19]. Incidences of chronic T2DM-related complications are associated to poor metabolic control, presence of related cardiovascular risk factors, and duration of disease [20]. T2DM is associated with chronic microvascular complications, including retinopathy, nephropathy, and neuropathy, and macrovascular complications, including coronary heart disease, peripheral vasculopathy, and cerebrovascular disease [21].

1.1 Background and Statement of the Problem

T2DM is associated with chronic microvascular complications, including retinopathy, nephropathy, and neuropathy, and macrovascular complications, including coronary heart disease, peripheral vasculopathy, and cerebrovascular disease [21].

ANN is considered an appropriate tool for the prediction of diabetes type2 with complications. Even though few studies exist on the prevalence of the disease, it is apparent that the diagnosis has helped to reduce the cases of the disease across the world. Other studies have noted that few people accomplish the diagnosis of diabetes type2, a limitation to this research. The US has experienced limitations in establishing studies that relate with

diabetes type2 with complications. The few studies that are linked with diabetes are generalized for the 2 types of diabetes. However, future research may help to relate to the present studies as well as establishing the truth in the studies. [166]. With timely diagnosis a major treatment problem with DT2M and related complications, use of ANNs presents remarkable prospects in diagnosis and treatment, which should undoubtedly inform further progression in research.

1.2 Objective and significant of the study:

The aims of the study were, first, to identify the key risk factors of diabetes with complications (diabetes type2 with ketoacidosis, diabetes type2 with hyperosmolarity, diabetes type with renal manifestations, diabetes type2 with ophthalmic manifestations, diabetes type2 with neurological manifestations, diabetes type2 with peripheral circulatory disorders).

Second aim was to develop an artificial neural network model for early prediction of diabetes type2 with complications. And to examine whether an artificial neural network model can effectively predict the likelihood of diabetes type2 with complications. Six years (2007, 2008, 2009, 2010, 2011 and 2012) of the Nationwide Inpatient Sample (NIS) data were used to investigate the association of these factors with diabetes type II complications.

This study tried to identify some key risk factors for those patients who are more likely to be diagnosed with diabetes type II complications. These risk factors were classified into four categories. First category, general factors include age, race/ethnicity. Genetic factors are the second category, which include family history of diabetes. Third category, lifestyle factors include obesity, smoking, alcohol abuse, and vitamin d

3

deficiency. Last category is chronic disease and surgical procedure which include hypertension, hypercholesterolemia, asthma, hyperlipidemia and hyperglyceridemia.

1.3 Research questions and hypothesis:

Question One: What are the different major risk factors associated with diabetes type2 with complications?

(H01). There are not a statistically significant combinations of risk factors that can differentiate and help predict different complications of type 2 diabetes.

(HA1). There are statistically significant combinations of risk factors that can differentiate and help predict different complications of type 2 diabetes

Question Two: Is artificial neural network a significant technique in predicting the risk of diabetes type2 with complications?

(H01). An artificial neural network model cannot be developed to accurately predict the risk of diabetes type2 with various complications.

(H02). An artificial neural network model can be developed to accurately predict the risk of diabetes type2 with various complications

Question Three: Does artificial neural network predict the risk of diabetes with complications better than logistic regression?

(H01). An artificial neural network model is not a better predictive model for determining the risk of diabetes with complications than a logistic regression model.

(H02). An artificial neural network model is a better predictive model for determining the risk of diabetes with complications than a logistic regression model.

1.4 Study Limitations

The Nationwide Inpatient Sample (NIS) data set does not include HbA1c test result. In addition, this study relied on the diagnosis codes that registered on NIS data. This study did not investigate some factors details such as alcohol consumption or smoking habit.

CHAPTER II

II. LITERATURE REVIEW

2.1 Diabetes Mellitus Overview

Diabetes mellitus is a multifaceted of metabolic disease typified by hyperglycemia that occurs as a consequence of defects in the secretion of insulin, action of insulin, or both [1,2]. It is a major public health problem across the globe due to the associated morbidity and mortality [3]. The chronic hyperglycemia in diabetes is linked to long-term dysfunction, damage, and failure of various organs, particularly the kidneys, heart, nerves, eyes, and blood vessels [1]. Rapid urbanization and lifestyle change have increased dyslipidemia and obesity prevalence, which have a critical role in diabetes development worldwide. Diabetes mellitus is a primary public health problem. The International Diabetes Federation (IDF) approximated that 382 million people had diabetes globally in 2013 [4], and this is projected to increase to 439 million by 2030 [5].

Diabetes is also a major public health problem in the United States. In 2012, it was reported that 29.1 million people or 9.3% of the U.S. population (all ages) had diabetes. It is estimated that 21.0 million people were diagnosed and 8.1 million were undiagnosed, implying that 27.8% of individuals with diabetes are undiagnosed. Among these cases, 28.9 million were in people aged 20 years or older. Approximated 208,000 individuals

aged younger than 20 years have diabetes in the United States. This is representative of 0.25% of all people in this age group [6]. The proportion of diagnosed and undiagnosed diabetes among individuals aged 20 years or older in the United States is summarized in table 1. With regard to race/ethnicity in the United States, the prevalence of diabetes is highest among the American Indians/Alaska Natives (15.9%), followed by Non-Hispanic Blacks (13.2%), Hispanics (12.8%), Asian Americans (9.0%), and Non-Hispanic Whites (7.6%) (See table 2). In 2012, it is estimated that there were 1.7 million new diabetes cases in people aged 20 years and older (Table 3). Approximately 23,525 new cases of diabetes are diagnosed among individuals younger than 20 years in the United States annually [6].

Table 1: Diagnosed and undiagnosed diabetes among people aged 20 years or older, United States, 2012

	Number with diabetes (millions)	Percentage with diabetes (unadjusted)
Total		
20 years or older	28.9	12.3
By age		
20-44	4.3	4.1
45-64	13.4	16.2
65 years or older	11.2	25.9
By sex		
Men	15.5	13.6
Women	13.4	11.2

Source: 2009–2012 National Health and Nutrition Examination Survey estimates applied to 2012 U.S. Census data.

Table 2: Age-adjusted percentage of people aged 20 years or older with diagnosed diabetes, by race/ethnicity, United States, 2010–2012

Race/Ethnicity	Percentage (adjusted)
Non-Hispanic white	7.6
Asian Americans	9.0
Hispanics	12.8
Non-Hispanic blacks	13.2
American Indians/Alaska Natives	15.9

Source: 2010–2012 National Health Interview Survey and 2012 Indian Health Service's National Patient Information Reporting System.

Table 3: New cases of diagnosed diabetes among people aged 20 years or older, United States, 2012

	Number of new diabetes cases	Rate of new diabetes cases per 1,000 (unadjusted)
Total	1.7 million	7.8
By age		
20-44	371,000	3.6
45-64	892,000	12.0
65 years or older	400,000	11.5

Source: 2010–2012 National Health Interview Survey, 2009–2012 National Health and Nutrition Examination Survey, and 2012 U.S. Census data.

The economic burden of diabetes is also enormous. In 2009, the estimated economic costs attributed to diabetes in the United States was $245 billion of which $176 billion is attributed to direct medical costs and $69 billion is attributed to indirect costs, including work loss, disability, and premature mortality [6]. In 2011, this burden increased with the IDF estimating that diabetes alone accounted for USD 465 billion in healthcare expenditures, with 11% of all healthcare expenditure being among adults aged between 20

and 79 years [6]. Thus prevention and management approaches are urgently required to curtail this worldwide pandemic [4].

Various pathogenic processes are implicated in diabetes mellitus, ranging from autoimmune pancreatic beta-cell destruction with subsequent insulin deficiency to abnormalities that occur as a consequence of resistance to insulin action. The basis of diabetes-associated abnormalities in fat, protein, and carbohydrate metabolism is deficient action of insulin on target tissues. The deficiency in the action of insulin is a consequence of inadequate secretion of insulin and/or diminished response of tissues to insulin in one or more points in the multifaceted hormone action pathways. Insulin secretion impairment and insulin action defects may coexist in the same patient, and in such a situation, it may be difficult to ascertain which abnormality, if either alone, is that major cause of hyperglycemia [7].

Diabetes is classified into various categories, including type 1diabetee mellitus (T1DM), type 2 diabetes mellitus (T2DM), gestational diabetes mellitus (GDM), and specific types of diabetes as a consequence other causes such as drug-or chemical-induced diabetes (e.g. following organ transplant or HIV/AIDS treatment), exocrine pancreatic disease (e.g. cystic fibrosis), monogenic diabetes syndromes (e.g. neonatal diabetes and maturity-onset diabetes of the young [MODY]) [8]. GDM was initially defined as any extent of glucose intolerance first recognized during pregnancy irrespective of whether it predated the pregnancy or persisted following the pregnancy. Currently, GDM refers to diabetes whose diagnosis occurs in the second or third trimester of pregnancy, and that is not typically overt diabetes [8]. It is estimated that GDM complicates approximately 7%

of all pregnancies (range of 1 to 14% based on the diagnostic tests used and the population studies), resulting in over 200,000 cases yearly [1].

Both the incidence and prevalence of T2DM are increasing globally due to increased rates of obesity and changes in lifestyle. The healthcare system attendant economic burden is skyrocketing due to the costs linked to treatment and diabetes-associated complications. T2DM remains the leading cause of blindness, cardiovascular disease, amputations, end-stage renal failure, and hospitalizations. It is also linked to increased risk of serious psychiatric illness, cancer, accelerated arthritis, chronic liver disease, cognitive decline, and other conditions associated with significant morbidity and mortality [9]. T2DM has been associated with increased risk of premature mortality in the population and majority of these mortalities are associated to CVD. Diabetes increases the hazards linked to other risk factors for CVD development, including hyperlipidemia, hypertension, and renal impairment. Similarly, in CVD patients, diabetes renders greater risk of worse outcomes, particularly when associated with complications, including retinopathy, neuropathy, and nephropathy. On the other hand, in patients with diabetes as the only risk, the population attributable risk of mortality may not be as high [10].

T1DM is a chronic autoimmune disease that precipitates in genetically susceptible persons by environmental factors. The β-cells of the islets of Langerhans of the pancreas are attacked by the body's own immune system, damaging or destroying them sufficiently to reduce and ultimately eliminate the production of insulin [11]. Type I diabetes mellitus accounts for approximately 5-10% of all diabetes cases. It is also referred to as insulin dependent diabetes [1]. T1DM often starts in individuals aged younger than 30 years is

thus also referred to as juvenile-onset diabetes. Even though T1DM can occur at any age [11], most of the cases are diagnosed at the age of 4 to 5 years, in teenage or early adulthood [2]. Type I diabetes mellitus is a consequence of cellular-mediated autoimmune pancreatic β-cell destruction. T1DM prevalence is reported to be about 20 million people globally. In the United States, the prevalence of T1DM among individuals aged 0-19 years is reported to be 1.7/1,000 [1].

The incidence of T1DM has been in the rise in the past decades reaching up to 5.3% yearly in the United States, implying that the event that is implicated in the onset is increasingly affecting individuals who are susceptible [11]. The steepest rise in the incidence of T1DM has been reported among individuals aged below 5 years [2]. The search for factors that trigger T1DM has been on for decades and so far only indirect evidence has emerged, mainly implicating some viral infections. It has been well established that a certain genetic constitution is necessary for diabetes to result from such an event. Nonetheless, concordance rates between dizygotic twins are only to approximately 10% while between monozygotic twins to only 50%. With prolonged follow-up, most discordant identical twins of TIDM patients finally get to express anti-islet autoantibodies progress to diabetes, albeit the second twin may express anti-islet autoantibodies 30 years following development of diabetes by the first twin. Thus is appears that genetic vulnerability persists for life, and that a log prodrome of anti-islet autoantibody expression measured in years generally precede progression to diabetes [11].

Even though the monozygotic twin concordance rate is higher than was previously imagined, it is below unity, and there have been strong disagreements with regard to the

time T1DM takes to develop. This suggests a strong environmental component as contributory to T1DM development [11]. Clinical disease onset is indicative of end stage destruction of β-cells resulting in T1DM. As an autoimmune disease, T1DM is typified by various features, including accessory and immune-competent cell presence in infiltrated islets; link of disease susceptibility to the class II genes of the major histocompatibility complex; islet cell specific antibody presence; T cell mediated immunoregulation (specifically in CD4+ cell compartment) alterations; interleukin producing TH1 cell and monokine in the disease process; immunotherapy response; and frequent other specific autoimmune disease occurrence in the patient of their family members [2].

The pathogenesis of selective destruction of β-cells within the islet in T1DM is challenging to follow because of pancreatic lesion heterogeneity. During the onset of overt hyperglycemia, a mixture of pseudoatrophic islets with cells producing pancreatic poly-peptide (PP cells), somatostatin (d cells), and glycogen (a cells), normal islets, and islets containing both infiltrating monocytes and lymphocytes, and b-cell are sometimes evident [7]. Lymphocytic infiltration occurs only in the residual β-cells that contain islet, and there is a possibility that the chronicity surrounding T1DM development is reflective of islet lesion heterogeneity [2]. Islet antigen-specific CD4+ T cell activation seem to be absolute prerequisite for T1DM development. Clones of CD4+ islet specific T-cells have been shown to induce diabetes and insulitis in mice, implying that CD4+ cells could be the sole immunocompetent cells needed in the disease process [2].

The autoimmune pancreatic β-cell destruction causes insulin secretion deficiency in the metabolic alterations linked to T1DM. Additionally, pancreatic α-cell function

becomes abnormal with associated excessive glucagon secretion in patients with T1DM. Usually, hyperglycemia results in reduced secretion of glucagon; nonetheless, in T1DM patients, hyperglycemia does not suppress the secretion of glucagons. The consequent abnormally elevated levels of glucagon worsen the metabolic defects because of insulin deficiency [5]. The commonest manifestation of this disruption in metabolism is the rapid development of diabetic ketoacidosis by patients with T1DM when insulin is not administered. Even though the major defect in T1DM is insulin deficiency, a defect in insulin administration also occurs. Various biochemical mechanisms have been implicated in the impaired response of tissues to insulin. Insulin deficiency results in uncontrolled lipolysis and increased fatty acid levels in plasma, thereby suppressing the metabolism of glucose in peripheral tissues, including skeletal muscle. This causes impairment in the utilization of glucose. In addition, insulin deficiency decreases the expression of various genes required normal insulin response by target tissues [2].

2.2 Type 2 Diabetes Mellitus with No Complications

T2DM primarily occurs when insulin secretion from the islets is unable to match the heightened insensitivity to circulating insulin action on target tissues, including liver, fat, and muscle. It is a heterogeneous disease occurs as a consequence of genetic factors, insulin resistance, and environmental factors, including sedentary lifestyle, over eating, stress, obesity, and aging. It is not autoimmune and the genes implicated in its causation have not been clearly identified in a majority of the patients [2]. T2DM is typified by sustained plasma glucose level elevation [12]. T2DM is the predominant type of diabetes accounting for 90-95% of all diabetes mellitus cases [2, 4]. The global rise in T2DM

signifies a major public health problem. T2DM was estimated to affect 366 million people in 2011, and this number is likely to increase to 552 million by 2030 [12]. It is also estimated that approximately 175 million cases of T2DM are undiagnosed globally [13]. The rapid rise in prevalence is attributed to escalated economic growth and changes in lifestyle in both developing and developed countries. This translates to a yearly growth of 2.7%, exceeding by a factors of 1.7 that of the world population. The proportion of excess mortality attributed to T2DM globally is approximated to be 7% [12]. T2DM incidence increases with age, with diagnosis of majority of the cases occurring after the age of 40 years [2].

The pathogenesis of T2DM is multifactorial. Under normal physiological conditions, the concentration of plasma glucose is kept within a narrow margin despite wide demand and supply fluctuation, through a dynamic and tightly controlled interaction between insulin tissue sensitivity (particularly in the liver) and insulin secretion. In T2DM, these mechanisms are impaired, with the result that the two primary pathological defects are impaired secretion of insulin due to pancreatic β-cell dysfunction, and impaired action of insulin due to insulin resistance [2] T2DM may present with combinations of characteristic symptoms, including polyphagia, polydipsia, polyuria, glycosuria, weight loss, and lethargy. The symptoms are reflective of the underlying diabetes pathophysiology of peripheral insulin resistance coupled with inadequate secretion of pancreatic insulin. Many patients with diabetes may be asymptomatic, but in the long term, uncontrolled hyperglycemia is likely to result in severe microvascular and macrovascular complications [14]. T2DM is thought to have a stronger genetic link than T1DM. T2DM affects 1-2% Caucasians, but its prevalence has been shown to be relatively higher in certain ethnic

groups, including Arabs and Pima Indians, implying that genetic factors have a major role than environmental factors [2].

T2DM meets several of the criteria for screening suitability. Its prevalence is increasing and it exerts considerable burden of health service use and suffering. The long latent disease period, the high fraction of undiagnosed cases, and the high fraction of people with complications at diagnosis are powerful arguments for screening for diabetes [15]. Undiagnosed T2DM is likely to occur in more than 2.8% of the general adult population, and this proportion increases to more than 10% in certain populations. Hyperglycemia tests can identify these people, majority of whom are likely to have, or are at risk for complications that are preventable [16]. Fasting plasma glucose (FPG) and/or glycated hemoglobin (A1C) are the recommended tests for screening. However, a 75 g oral glucose tolerance test (OGTT) should be used when FBG is 6.1-6.9 mmol/L and/or A1C is 6%-6.4%. It may also be recommended when FPG is 5.6-6.0 mmol/L and/or A1C is 5.5%-5.9%, and when T2DM or IGT are highly suspected [16].

The recommendation by the American Diabetes Association is that, individuals who are overweight or obese (BMI ≥ 25 kg/m2) and who have extra risk factors for diabetes, including ethnicity/race (for instance Latino, African American, Pacific Islander, Asian American, and Native American), history of polycystic ovarian disease, or family history of T2DM, should be screened. Diagnosis for individuals who are asymptomatic needs two abnormal test results [3]. This can be from different tests on different days or on the same or from the same test on different days. A test that come abnormal test should be repeated on a different day. If the repeated test returns abnormal again, a diagnosis of

diabetes is made. For a patient with typical hyperglycemia symptoms, including polydipsia, polyuria and weight loss, can be diagnosed through random plasma glucose of ≥ 200 mg/dL or higher [2]. In such a case, no repeat measurement is required. T2DM patients often present with hyperglycemia and overweight, with gradual symptom onset including blurred vision, fatigue, polyuria, and polydipsia [4]. Islet cell antibody (ICA) with reflex to glutamic acid decarboxylase antibody (GADA) testing should be considered for differential diagnosis for children and teenagers to differentiate early T1DM from T2DM and for adults who are not overweight and are not responding to lifestyle modification and oral hypoglycemic. Persons without the above risk factors should have testing commenced at the age 45 years, and if the tests are normal, they should be repeated at least every three years [17].

The effectiveness of early diabetes identification through mass screening of individuals who are asymptomatic relative to no screening is yet to be established. Nonetheless, diabetes attains the criteria for disorders that require early detection. Screening should be sequential rather than a one-time event [18]. The cost-effectiveness of various strategies for screening individuals who are asymptomatic has been compared with strategies for screening individuals following diabetes or cardiovascular disease development [16]. It was assumed that individuals diagnosed with diabetes would be treated afterwards using the same approaches as those currently used for diabetic individuals in the United States to prevent microvascular and cardiovascular events. Six of the simulated approaches were population-based rather than targeting populations at high risk. The analysis revealed that opportunistic screening strategies coupled with lipid testing and blood pressure measurement demonstrated the lowest cost per quality-adjusted life-

years. It was concluded that using a risk assessment strategy prior to formal screening is likely to improve cost-effectiveness. Therefore, the recommendation is that diabetes screening should be incorporated into lipid tests and screening for hypertension [18].

Pre-diabetic individuals, particularly those with IGT or an A1C of 6.0 – 6.4% have a heightened risk of developing T2DM as well as macrovascular complications. Such individuals are likely to benefit from strategies that reduce cardiovascular risk factors [6]. Individuals of ethnic populations are at high-risk should be screened for pre-diabetes and T2DM through the recommended screening tests, including OGTT, A1C, and FPG. Nonetheless, the high hemoglobinopathy prevalence among these population is likely significantly reduceA1C accuracy as a reliable tool of screening in these individuals. Additionally, high-risk ethnic groups are likely to have slightly higher A1C levels than Caucasians at the same level of glycemia, and additional studies are likely to assist in determining ethnic-specific A1C thresholds for the diagnosis of diabetes [16].

For effectiveness, the coverage of population-based screening should wide and the goal should be early diagnosis and consequent intervention to minimize morbidity and mortality [5]. Even though relatively low diabetes prevalence in the general population reduce the chance of cost effectiveness of mass screening, diabetes testing in individuals with T2DM risk factors or with diabetes-associated comorbidities is likely to lead to more benefit than harm, with subsequent overall cost savings. Therefore, routine testing for T2DM is justifiable in some but not all settings. Screening persons aged as early as 40 years in the offices of family physicians has proved useful in unrecognized diabetes detecting [16].

2.3 Diabetes Mellitus Type 2 with Complications

The current increasing concern that T2DM attracts is attributed to the serious consequences caused by both the disease itself and its associated multi-systemic complications. The chronic complications associated with T2DM not only trigger escalating burden to the national health systems and heighten the rate of diabetes-associated morbidity, but also lead to untimely mortality and reduced quality of life [19]. Incidences of chronic T2DM-related complications are associated to poor metabolic control, presence of related cardiovascular risk factors, and duration of disease [20]. T2DM is associated with chronic microvascular complications, including retinopathy, nephropathy, and neuropathy, and macrovascular complications, including coronary heart disease, peripheral vasculopathy, and cerebrovascular disease [21].

Diabetes ketoacidosis (DKA) is a complication of T2DM. DKA is typified by a triad of metabolic acidosis, uncontrolled hyperglycemia and increased concentration of ketones in the body. DKA is a serious acute hyperglycemia emergency as well as the number one cause of mortality in patients with diabetes [22]. The case fatality rate for DKA varies from 1 to 5% [23]. Even though the highest mortality rate occurs in older adults and patients with comorbid conditions, DKA is the leading cause of mortality in diabetic individuals who are younger than 24 years, mostly due to cerebral edema. Approximately 27 to 37 percent of DKA cases occur in individuals with newly diagnosed diabetes [24]. DKA was initially the hallmark of a life-threatening medical emergency in patients with newly diagnosed or poorly controlled T1DM. In the past two decades, however, this usual

relationship has been challenged with increasing reports showing increased prevalence of DKA in T2DM patients [25].

Several reports have shown that children and adolescents with obesity and presenting with unprovoked DKA manifest metabolic, immunological, and clinical features of T2DM. They often present acutely with a few days or weeks of polydipsia, weight loss, and polyuria. Despite their presentation with ketoacidosis, these children are likely to achieve near-normoglycemia remission and discontinue insulin. The remission can last for months to years during which acceptable glycemic control is achieved using oral agents or diet. The variant of diabetes is often referred to as ketosis-prone T2DM in literature [22]. DKA is generally less common in T2DM compared to T1DM because patients with T2DM are generally regarded insulin resistant and not insulin deficient (Lin et al. 2009). The prevalence of DKA in patients with T2DM is estimated to range from 4% to 29% depending on ethnicity/race [26].

The occurrence of DKA in patients with T2DM is commonly linked to extreme stress situations, but there is no clear association between a specific precipitant and DKA development. The commonest causes of DKA development include non-adherence to therapy or inadequate insulin treatment, followed by new diabetes onset [25]. Acute illnesses and certain medications are also potential significant causes. Three mechanisms of DKA in T2DM have been proposed: a) Counter regulatory stress hormone elevation, b) insulinopenia, and c) free fatty acid elevation. Some researchers have argued that insulinopenia is the only significant mechanism in patients with T2DM [24]. The stressors that precipitate to DKA are thought to cause a relative rather than definitive insulin

deficiency. Potential causes for this relative deficiency of insulin included impaired secretion of insulin because of chronic exposure of islet or insulin secreting cells to high glucose free fatty acid levels [25].

The insulin deficiency triggers the increase in counter regulatory hormones, including catecholamines, glucagon, growth hormone and cortisol. With the inability to utilize glucose, the body requires alternative sources of energy. Subsequently, there is increase in lipase activity causing adipose tissue breakdown thereby yielding free fatty acids. These components are converted to acetyl coenzyme A, which is partially utilized for energy production in the Krebs cycle; the remainder is broken down into ketones, which can be utilize for energy, but often accumulate rapidly. Proteins and glycogen become catabolized for form glucose. Combined, these factors facilitate hyperglycemia, which causes osmotic diuresis and subsequent metabolic acidosis, dehydration, and hyperosmolar state [24].

Other causes of DKA include prolonged fasting, which increases the likelihood of ketosis and potentially decreases the secretion of insulin, and hypokalemia, which is likely to impair the secretion of insulin. Intensified diabetic management in T2DM patients with DKA leads to considerable improvement in insulin sensitivity and beta-cell function with subsequent discontinuation of insulin. Even though fatty acid and counter-regulatory stress hormone elevation are proposed mechanisms, plasma concentrations of the free fatty acids and stress hormones have not shown any significant difference in ketosis prone and non-ketosis prone T2DM. This has led to the belief that the predominant mechanism for ketosis in patients with T2DM is the decrease or deficiency in insulin secretion [25].

T2DM is associated with high prevalence of kidney disease. Moderate to severe impairment in renal function (eGFR < 60 mL/min) occurs in about 20-30% of patients. Persons with progressive renal dysfunction have an elevated risk for hypoglycemia, which is often multifactorial [9]. Renal disease is an especially devastating complication because of the associated significant reductions in both quality and length of life. Various forms of renal disease can be observed in diabetic patients such as diabetic nephropathy and hypertension and vascular disease-associated ischemic damage. Diabetic nephropathy is associated with progressive increased proteinuria with subsequent decline in renal function culminating in end stage renal disease (ESRD). The major risk factors for diabetic nephropathy include poor glycemic control, long diabetes duration, male gender, hypertension, cigarette smoking, and obesity [9, 27].

The earliest stage of diabetic nephropathy is associated with hyper-filtration where there is significantly higher glomerular filtration rate (GFR) than normal. Nonetheless, hyper-filtration identification may not be clinically useful, and it may be difficult to determine through routine tests. On the other hand, persistent albuminuria is regarded the earliest diabetic nephropathy clinical sign [24]. Initially, there is leakage of small albumin amounts that are below urine dipstick detection threshold. This stage is termed "microalbuminuria", which can then worsen to the extent that there is sufficiently high excretion of urinary albumin that can be detected by urinary dipstick, a stage termed "overt nephropathy". The progression rate from norm-albuminuria to microalbuminuria and to overt nephropathy is often slow, characteristically taking five years or longer for progression through each stage [27].

In the early diabetic retinopathy stages, the rate of renal function loss is fairly slow (1 to 2 mL/min/1.73 m2 annually) and not impressively higher compared to that of the general population (0.5 to 1 mL/min/1.73 m2 annually). Nonetheless, the late overt nephropathy stage is associated with accelerated rate of renal function decline (5 to 10 ml/min/1.73 m2 annually) [27] (Figure 1). Therefore, considerable renal dysfunction is often not evident until the late course of diabetic nephropathy [22]. It is worth noting that progression rate can differ between individuals, and that disease clinical markers (eGFR, urinary levels of albumin) may not always correlate well with renal disease severity evident on biopsy. In addition, aggressive glycemic and blood pressure control as well as using renal protective medication can stop of slow diabetic nephropathy progression [27].

Stage of Nephropathy
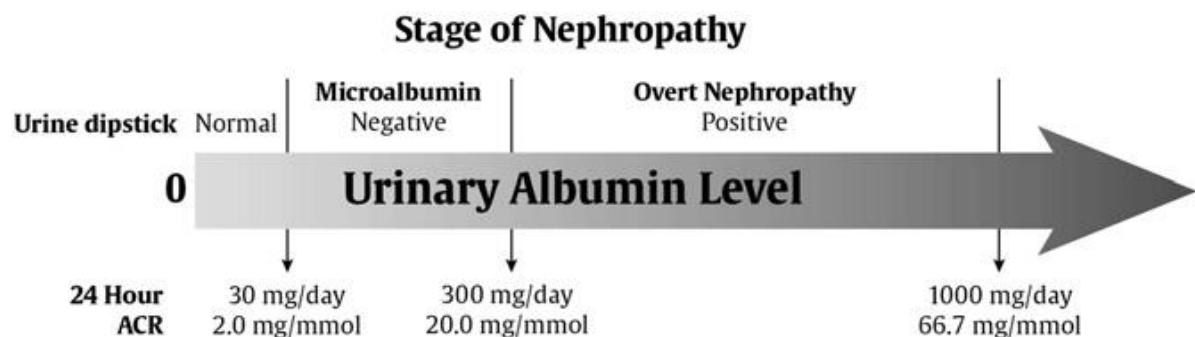
Figure 1: Level of urinary albumin by various test methods and stage of diabetic nephropathy. ACR means albumin-to-creatinine ratio (McFarlane et al. 2013, p. 130).

Patients with T2DM have a higher likelihood of developing some form of disease of the eye. The leading causes of blindness in these patients include diabetic retinopathy, glaucoma, cataract, optic nerve atrophy, age-related macular degeneration, and macular edema [28]. The most serious ophthalmic/ocular complication linked to T2DM is diabetic retinopathy, which is also one of the commonest causes of secondary blindness [19]. Diabetic retinopathy is associated with devastating effects on life due to the progressive

visual impairment, blindness, and reduced quality of life [29]. It is acknowledged as the commonest cause of new cases of legal blindness among individuals of working age. The prevalence of diabetic retinopathy ranges from 15.3% to 42.4% in various epidemiologic studies. The crude prevalence rate of diabetic retinopathy among the adult population in the United States is reported to be 40.3%; the rate of sight-threatening retinopathy is 8.2% [30].

Various studies have reported that both modifiable risk factors, including blood pressure, blood glucose, smoking, and serum, and non-modifiable risk factors, including age, ethnicity, genetic predisposition, and duration of disease, play a role in influencing the development of diabetic retinopathy [19]. Factors associated with progression of diabetic retinopathy include elevated glycated hemoglobin (A1C), longer duration of diabetes, dyslipidemia, increased blood pressure, proteinuria, low levels of hemoglobin, and severe retinopathy itself. Visual loss is linked to considerable morbidity, including increased hip fracture, falls, and a four-fold increase in mortality [30].

Diabetic retinopathy is clinically diagnosed, defined, and treated based exclusively on the degree of retinal vascular disease [29]. Three distinct types of diabetic retinopathy have been identified: a) macular edema, which include focal or diffuse macula vascular leakage; b) retinal capillary closure, a kind of vascular change detected on fluorescein angiography, and is also well acknowledged as a likely blinding diabetic complication without any available treatment options; and c) progressive accumulation of changes in blood vessels that include vascular tortuosity, intraretinal hemorrhage, vascular malformation, and micro-aneurysms (together termed non-proliferative diabetic

retinopathy) that eventually results in abnormal growth of vessels (proliferative diabetic retinopathy) [30]

The clinical signs of diabetic retinopathy have been grouped into background and proliferative stages [31]. Background retinopathy includes features such as small hemorrhages that occur in the middle retinal layers. Clinically, they appear as "dots" and thus often termed "dot hemorrhages". Hard exudates are a consequence of lipid deposition that primarily occurs at the margins of the hemorrhages. Retinal edema may be a consequence of microvascular leakage and is suggestive of blood-retinal barrier compromise. It appears as grayish areas in the retina. Intervention may be required for retinal edema because it is sometimes linked to visual deterioration. Micro-aneurysms are small vascular dilatations in the retina, and are mostly the first sign of retinopathy. Clinically, they appear as red dots during retinal examination [32]. Proliferative retinopathy is typified by new blood vessel formation on the retinal surface potentially resulting in vitreous hemorrhage. White retinal areas ("cotton wool spots") can be suggestive of impending proliferative retinopathy. As retinopathy progresses, blindness may ensue as a consequence of traction retinal detachment and vitreous hemorrhage. Visual loss is likely to occur in the absence of intervention [32].

Conventional classifications subdivide diabetic retinopathy into five stages, including non-proliferative, pre-proliferative, proliferative, partial or total retinal detachment, diabetic retinopathy, and secondary neovascular glaucoma. Non-proliferative is a reversible stage typified by changes in blood vessels in the ocular fundus such as hard exudates, hemorrhages, maculopathy, and microaneurysms. Poor glycemic control with

frequent hyper- and hypoglycemia fluctuations, combined with arterial hypertension contribute to the progression of non-proliferative diabetic retinopathy to more advanced stages. In T2DM, symptoms of diabetic retinopathy are registered in 15-30% of cases at the same time of diagnosis of diabetes. This escalated occurrence of symptoms of diabetic retinopathy directly on diagnosis of diabetes is because T2DM is generally diagnosed later than T1DM when the harmful effect of hyperglycemia on nerves and blood vessels has progressed unnoticed for a long period. It is estimated that 50-70% of cases of T2DM manifest the symptoms of diabetic retinopathy after ten years and about 90% of these patients after thirty years [31].

While cataract and glaucoma usually occur in non-diabetic individuals, diabetic patients have a 60% higher risk of developing cataract and 40% chance of being diagnosed with glaucoma [30]. T2DM is particularly associated with increased risk of cortical cataract and posterior subcapsular cataract. The incidence of cataract has been approximated to be 3.31 per 1,000 person-years of T2DM patients [33]. Glaucoma is a consequence of increased internal eye pressure and poor circulation within the optic nerve, which results in progressive optic nerve damage with subsequent irreversible loss of peripheral vision loss, and ultimately to central vision loss [19]. Cataract is the presence of clouding/opacity in a portion of the clear lens of the eye, which then obscures vision. It is a leading cause of blindness globally. Diabetes causes damage to the eye and vision impairment over time by causing swelling of the lens of the eye, and ultimately to cataract formation. In both conditions, there is progressive vision loss over time with worsening of the condition [33].

Hyperosmolar hyperglycemic state is a common, life-threatening endocrine emergency, and a major complication of T2DM. It occurs in all age groups, but is mostly common in older adults with T2DM. The hallmark of hyperosmolar hyperglycemic state is marked hyperglycemia, profound dehydration, and often some extent of neurologic impairment without or with mild ketosis [5]. Generally, hyperosmolar hyperglycemic state and diabetic ketoacidosis have been identified as distinct entities; nonetheless, approximately one third of patients display findings of both conditions. Several processes are implicated in the pathophysiology of hyperosmolar hyperglycemic state. Glucosuric diuresis is the event that initiates hyperosmolar hyperglycemic state. Glucosuria causes impairment of the kidney's concentrating capacity, thereby further exacerbating water loss [34]. Under normal physiological conditions, the kidneys function as a safety valve for eliminating glucose above a given threshold and prevent further accumulation. Nonetheless, underlying renal disease or decreased intravascular volume can decrease the glomerular filtration rate, resulting in increased glucose level. The excessive loss of water relative to sodium causes hyperosmolarity. Insulin is available, but not sufficient to reduce the levels of blood glucose, especially when there is significant insulin resistance [34].

The factors that precipitate hyperosmolar hyperglycemic state may include medications, infections, undiagnosed diabetes, noncompliance, coexisting diseases, and substance abuse [2]. Infections such as urinary tract infection, pneumonia, and sepsis are the commonest triggers of hyperosmolar hyperglycemic state. Poor compliance with diabetic medications is also a common cause [34]. The mortality rate associated with hyperosmolar hyperglycemic state varies from 10 to 50%, a rate that is significantly higher than that of diabetic ketoacidosis (1.2 to 9%). Nonetheless, the true mortality data are

challenging to interpret due to the high incidence of diabetes-related co-morbidities. Strong fatal outcome predictors include degree of dehydration, age, underlying precipitating causes, hemodynamic instability and degree of consciousness [34].

Diabetes and vascular disease have an intimate association and share pathophysiological characteristics. The increasing diabetes rates also influence the prognosis and prevalence of peripheral artery disease. T2DM has been shown to increase critical limb ischemia incidence four-fold in patients with peripheral artery disease [35]. Peripheral vascular disease (PVD) is typified by progressive reduction in blood flow in one or more limbs due to atherosclerosis. PVD is a major risk factor for amputation of decreasedextremity, and mostly coexists with coronary artery disease (CAD), cerebrovascular disease (CVD), and thus, is linked to poor prognosis and increased risk of mortality and morbidity. PVD commonly occurs in people with T2DM and has been shown to occur about three times more frequently in diabetic individuals compared sex- and age-matched non-diabetic individuals. Risk factors that contribute to PVD development include male gender, hypercholesterolemia, cigarette smoking, hyperglycemia, and advanced age [19]. Functional changes, including flow-mediate dilation and arterial stiffness occur initially in the arteries, resulting in the loss of elasticity, whereas structural alterations such as foam cell formations and fatty degeneration occur later with resultant intimamedial thickening, formation of plague and to artery clogging causing interference with blood flow [4]. The plaque finally ruptures with subsequent intraluminal thrombosis that leads to end points such as CVD, PVD, and CAD. PVD is correlated with other T2DM-associated complications [35].

An association exists between retinopathy and impaired peripheral arterial circulation of the decreased limbs independent of major cardiovascular risk factors. Studies assessing the correlation of peripheral arterial disease, diabetic nephropathy and diabetic retinopathy in T2DM have shown that the presence of both albuminuria and retinopathy in the same patient heightens cardiovascular disease risk 8.9 times [35]. Since neuropathy also has a microvascular aspect, structural microvasculature damage can ultimately result in nerve dysfunction, which is a critical in peripheral nerve injury pathogenesis. It is increasingly being acknowledged that smaller vessels are likely to become similarly damaged resulting in poor circulation in the extremities and eventually to peripheral neuropathy [36]. Peripheral artery disease progresses more rapidly and results in worse outcomes in patients with T2DM than patients without diabetes. Patients with T2DM and peripheral artery disease have been shown to be at a higher risk of mobility loss, amputation, functional impairment, and cardiovascular mortality. High HbA1c levels are independently linked to increased peripheral artery disease risk in patients with T2DM, implying that poor glycemic control could be a risk factor for peripheral artery disease. Studies suggest that treatment with insulin sensitizers is likely to reduce peripheral artery disease risk in patients with T2DM [37].

Cardiovascular disease is also a major complication of T2DM. T2DM patients have been shown to have twice the risk of developing cardiovascular disease relative to the general population of the same sex and age, and that this risk is constant after adjusting for other traditional cardiovascular risk factors. Additionally, cardiovascular disease is acknowledged as the leading cause of mortality in 80% of diabetic patients compared to 30% in the general population [38]. The excess mortality has been shown to be higher in

women compared to men, and life expectancy has been demonstrated to be shortened by seven to ten years. The incidence of cardiovascular complications has been linked to longer disease duration, poor metabolic control and the presence of other traditional cardiovascular risk factors, albeit these factors contribute only a part of this heightened cardiovascular risk. Decreasing this excess cardiovascular risk and improving prognosis require early and aggressive management of T2DM [38]. T2DM is associated with increased frequency of atherosclerosis development, which increases the risk of coronary artery disease (CAD). Hyperglycemia is also likely to exacerbate myocardial ischemia and cause dysrhythmias [9]. T2DM is also associated with increased risk of incident heart failure and stable angina. Coronary artery disease (CHD), angina pectoris, myocardial infarction, and sudden death have been shown to be at least two-fold more common in T2DM patients compared to no-diabetic patients. A high proportion of T2DM patients die following an acute myocardial infarction within 1 year, and a significant number of patients die outside the hospital. Relative risk for CHD events have been shown to be higher in female patients with T2DM than male patients with T2DM. The reason behind the sex variation is largely unclear, but is thought to be partly explained by a heavier risk-factor burden and a greater atherogenic dyslipidemia and blood pressure effect on cardiovascular disease risk in diabetic women compared to diabetic men [39].

2.4 Risk Factors for Type 2 Diabetes Mellitus

The etiology of T2DM is multifaceted and potentially involves various factors, most of which are not fully understood. T2DM is associated with several risk factors. Even though T2DM is linked to complications, it is a disease that can be prevented. Control of

diabetes requires the recognition of the associated risk factors. Susceptibility of an individual to develop diabetes is dependent on a collection of intrinsic factors the influence (1) the pancreatic beta cell capacity to produce insulin, (2) the amount of glucose that comes from the liver (gluconeogenesis) and the gut (digestion of food), (3) cellular insulin sensitivity, and (4) the degree to which glycogen is degraded (glycogenolysis) [40]. Risk factors associated with T2DM can be modifiable or non-modifiable risk factors. Non-modifiable risk factors are uncontrollable risk factors and include sex, age, genetic susceptibility, socioeconomic status, and other environmental factors. Modifiable risk factors are controllable risk factor and include lifestyle factors, hypertension, obesity, smoking, and dyslipidemia [41]. In part because T2DM is well acknowledged to have strong lifestyle and genetic determinants, most researchers have thought the it is a consequence of gene-environment interactions, with the environmental constituent relating mainly to lifestyle factors such as poor diet, obesity and physical inactivity. Nonetheless, there has been implication of a strong genetic component, with relatives of patients with T2DM being at a higher risk of developing it [40].

Some ethnic populations are also thought to be a heightened susceptibility to diabetes. In particular, South Asians have been found to have adverse patterning of body fat that may increase their susceptibility to insulin resistance [14]. Management of these risk factors is essential if the onset of T2DM is to be delayed or prevented and the occurrence of life-threatening complication is to be avoided [41]. Widespread challenges emerge when a large proportion of a population is diabetic because it has societal, economic, individual, and clinical impact. Thus, establishing the major risk factors and

their distribution in a particular population are essential for designing and implementing targeted intervention that can reverse or halt the future prospects [42].

The evidence the T2DM is strongly linked to genetic factors first emanated from family-based studies in which the observation that clusters of diabetes within groups of biologically related persons resulted in the quantification of diabetes heritability and familial risk. Having parents with diabetes was acknowledged to double T2DM risk [2]. Quantitative genetics that exploit information regarding familial relatedness and disease coalescence have been employed to approximate the degree to which genetic factors explain disease. "Broad sense" heritability approximations for T2DM show the total ration of the total genetic to the total environmental differences explained by these factors for a certain phenotype [5]. The search for precise genetic variants that trigger T2DM has been ongoing for decades. Linkage studies on genetic and family association have been employed to detect highly penetrant genetic loci [40]. The introduction of massively high throughput, parallel genotyping technologies and other variations on these arrays, coupled with very large case-control cohorts, and the willingness of close collaboration among geneticists, stimulated a quantum leap in T2DM loci discovery. Since TCF/L2 was discovered in 2006, over 100 independent genetic loci have been discovered and now reliably linked to T2DM or its quantitative metabolic traits, including insulin and glucose [41].

2.4.1 Age

T2DM prevalence has been found to increase with advancing age with most of the cases being diagnosed above the age of 40 years [43]. This is potentially attributed in part

to age-related abnormal glucose tolerance and decreased secretion of insulin. Insulin resistance and central obesity are common among the aging population and have been linked to metabolic diseases, including T2DM. However, the clear mechanism by which this age-related pancreatic beta cell function occurs is not clear. Increased body fat especially visceral adiposity, and decline in lean body mass that often increase with age and are likely to contribute to insulin resistance development. Aging has been found to induce decreased insulin sensitivity and inadequate or altered compensation of the functional mass of beta cells in the presences of increasing resistance to insulin. With regard to beta cell functions, aging is associated with decreased capacity of beta cell proliferation and enhanced apoptosis sensitivity. Aging triggers insufficient and altered beta cell functional compensation and decreased insulin sensitivity in presence of increasing insulin resistance [44].

Aging is thought to affect mitochondrial function. Usually, mitochondria function to generate the cell's supply of adenosine triphosphate (ATP), and play a role in a range of cellular processes. Mitochondrial dysfunction is critical to aging theories as age-related mitochondrial changes potentially impair various cellular physiological functions thereby contributing to development of various age-related diseases [45]. Increasing cellular oxidative stress from various causes triggers mitochondria and mitochondrial DNA (mtDNA) damage and results in mitochondria functional crisis, aging, and cell death. Aging itself is also associated with abnormal mitochondrial morphology and apoptosis or cell death [46]. Recently, there have been suggestions that age-related decline in mtDNA causes insulin resistance, thereby contributing to increased T2DM prevalence with advancing age [47]. In the United States, it is approximated that the proportion of

individuals aged 20 years or older with undiagnosed or diagnosed diabetes increased with age in 2005-2008. Approximately 3.7% of individuals aged 20-44 years had diabetes, and this number increased to 13.7% among individuals aged 45-64 years, and to the highest percentage of 26.9% among individuals aged ≥65 years. A similar trend was reported in England, where diabetes prevalence increased with age [6].

The peak diabetes prevalence is in the 65-74-year age group with 10.4% women and 15.7% men being affected. Several other studies have supported these findings. For instance, Suastika et al. [44] conducted a study on Bali population and demonstrated that T2DM prevalence was higher among the elderly compared to the individuals in the younger age group. It has been demonstrated that the first and second insulin secretion phases usually decrease at an estimated rate of 0.7% annually with aging. However, aging per se does not affect insulin sensitivity independent of body composition changes. Lean body mass decline and increased body fat especially visceral adipocytes (central obesity) that often occurs with aging is likely to cause insulin resistance. Aging is also associated with chronic inflammation, which also contributes to insulin resistance, and subsequently T2DM development [46].

T2DM was originally regarded as a disease affecting primarily adults. Nonetheless, in recent years, many of its cases have been reported in children and adolescents. Like in adults, the disease in children and adolescents is often asymptomatic and detection is mainly through screening [43]. In populations with high incidence, the prevalence is likely to be markedly higher among the younger adults aged 20-35 years while in others the prevalence and incidence increase primarily in older individuals aged 55-74 years [3]. In

American Indian adolescents and children, T2DM was initially described among the Pima Indians and there has been steady increase in the prevalence in the subsequent years. Reports of T2DM among adolescents and children in recent years have appeared from various ethnic groups, including Native Americans, African American, Mexican Americans, Asian Indians, Polynesians, Chinese, and Arabs from the Gulf States. It seems that T2DM is still relatively uncommon children and young adults of Caucasian background [44]. The increasing prevalence of T2DM in children and adolescents in largely linked to changes in lifestyle, including increased obesity prevalence among individuals within this age group. Increasing obesity severity has been directly related with increased IGTTN in children even after controlling for Tanner stage, race, and sex. Puberty is also thought to play a role in T2DM development among young individuals [48].

Puberty has been associated with increased levels of GH/IGF-1, which then results in insulin resistance and insulin-mediated glucose disposal. Puberty has also been linked to enhanced early and late responses to hyperglycemia resulting in hyperinsulinemia. Other factors that contribute to insulin resistance and subsequently to T2DM among children and adolescents include family history, ethnicity/race, and sedentary lifestyle [48]. An investigation of children in the age of 4-17 years without and with parental diabetes from childhood to adulthood found out that the BMI of children whose parents had diabetes was higher. These children also have elevated systolic blood pressure, increased triglycerides, increased insulin resistance index, increase fasting insulin and glucose, decreased high density lipoprotein, and increased low density lipoprotein in adulthood. Low birth weight has been linked to the thrifty gene hypothesis thereby explaining the decrease in functionality of beta cells and elevated fasting insulin [48].

2.4.2 Gender

T2DM incidence and prevalence vary to a certain extent between the sexes, but these variations are relatively small and seem to be attributed to differences in other risk factors, including physical activity, dietary habits, and obesity [49]. Literature shows some gender-specific variations in T2DM development. The waist-to-height ratio has been identified as an independent parameter for T2DM development in Chinese women but not men [50]. In the general population, men are often less obese but more prone to abdominal/central obesity, and thus demonstrate a more heightened risk of T2DM than women [51]. However, some researchers argue that even though there is some difference, both women and men gain more fat with age, and after the age of 60 years, there seems to be no gender differences in relation to age at diagnosis, implying that T2DM is likely to be more evenly distributed among women and men in advanced ages [52]. Literature suggests that at the same degree of obesity, men are generally more vulnerable to diabetes development than women. Obese men are also thought to more insulin resistant than women and this can explain the gender difference in T2DM development [51]. The higher likelihood of insulin resistance in men is attributed to more active visceral fat among people of this gender [52].

Some heterogeneity in T2DM determinants in the clinical phenotype has been established. Prior research demonstrates that more girls than boys have pediatric T2DM. Among adult patients, however, this association is reversed. The factors that influence this demographic difference have not been fully clarified [53]. Socioeconomic status seems to be a critical factor in T2DM development, particularly for the female gender. For instance,

in Hong Kong Chinese, the reported age-adjusted ration for developing diabetes was 4.5 in females with the lowest socioeconomic status relative to those with the highest socioeconomic status [54]. The corresponding age-adjusted odds ratio for males was 1.9. Among the Chinese rural residents, the prevalence of screen-detected diabetes, impaired fasting glucose, and previously diagnosed diabetes was considerable higher in women than men. Taken together, these results are likely to explain a female excess in the prevalence of T2DM in countries whose economy is poor [55].

2.4.3 Race/Ethnicity

Race/ethnicity appears to influence the risk of T2DM development. Certain races/ethnicities have been shown to be at a higher risk of T2DM development. In particular, racial/ethnic minorities in the United States have been shown to have a greater burden or higher prevalence of diabetes compared to whites. For instance, compared to non-Hispanic white Americans, the risk of diabetes is 77% higher among African Americans and 66% higher among Hispanic/Latino Americans [56]. The age-adjusted prevalence T2DM rates in adults aged 20 years or older appears to be higher among America Indian and Alaska Natives followed by African American, then Hispanics, and then Asian American. A disproportionate increase in T2DM prevalence rates among African American and Hispanics aged 20-74 years and who are overweight has been reported [52, 54].

Diabetic complication rates are also higher among the racial/ethnic minorities in the United Stated. African American have been shown to have higher prevalence rates for end stage renal disease, visual impairment, and mortality; Hispanics have been found to

have higher end stage renal disease and mortality rates; and American Indians have been found to have higher rates of mortality when compared with non-Hispanic whites [57]. These racial/ethnic variations are attributed to factors such as genetics, adiposity, waist circumference, fitness, insulin secretion and sensitivity, and inflammation, each conveying independent risk for diabetes. For instance, greater phase 1 insulin release has been demonstrated among African Americans and higher percentage body fat at any BMI among South Asians. Non-Hispanic Blacks have been demonstrated to have considerably decreased fractional body fat content at any BMI compared to Mexican American and non-Hispanic Whites. Fractional body fat content after adjusting for BMI has been shown to be higher in Asian Indians and lower in African Americans [58]

Age-adjusted* percentage of people aged 20 years or older with diagnosed diabetes, by race/ethnicity, United States, 2010–2012

Race/Ethnicity	Percentage
Non-Hispanic whites	7.6
Asian Americans	9.0
Hispanics	12.8
Non-Hispanic blacks	13.2
American Indians/Alaska Natives	15.9
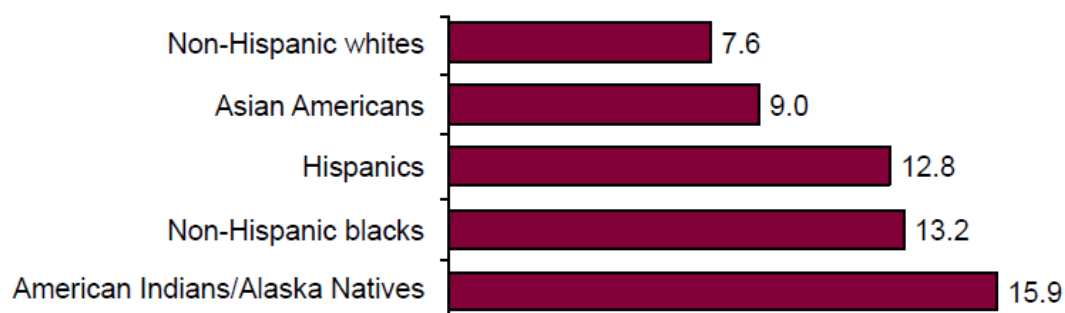
Figure 2: Racial and ethnic differences in diagnosed diabetes among people aged 20 years or older, United States, 2010–2012

Source: 2010–2012 National Health Interview Survey and 2012 Indian Health Service's National Patient Information Reporting System.

2.4.4 Household Income

Socioeconomic status seems to be associated with T2DM. In developed countries, the highest T2DM prevalence is found among people of lower social classes. It has been proposed that both structural factors and personal factors are likely to explain why T2DM

37

burden is higher among individuals with lower socioeconomic position. The burden of T2DM-associated complications has been shown to increase with declining socioeconomic position. The contrary seems to be the case in developing countries where the highest prevalence is found among people of the highest social class. Socio-economic status is thought to have an independent association with T2DM when different socio-economic groups are compared [42]. Skar et al. [42] compared the relationship between higher social class and T2DM in India and found out that affluence was related to increased T2DM risk. This finding supports various other studies that have explored the effect of socio-economic status on T2DM in developing countries. It is thought that this association is explained by obesity. This implies that in developing countries such as India, high social class cultivates a life-style linked to obesity, which predisposes the affluent to T2DM [5]. Life-style opportunities available seem to be dependent on the resources of an individual. Affluence assures better conditions in life and hence may be viewed as a proxy for social class. Additionally, affluence is associated with the accumulation of various factors, including higher calorie intake and physical inactivity, which also predispose to obesity [42]. The association between socioeconomic position and mortality in individuals with T2DM and without T2DM has been explored. It has been demonstrated that all-cause mortality increases with decreasing socioeconomic position in both groups [59].

2.4.5 Smoking

Smoking is associated with devastating and indisputable damage on public health. Tobacco smoking is acknowledged as the most important causes of preventable mortality and morbidity globally, contributing to 1 in 10 deaths among adults globally [17]. Tobacco

smoking is acknowledged as an independent, modifiable risk factor for T2DM. Smoking has been shown to increase the incidence of T2DM. Compared with nonsmokers, both former and current smokers have been shown to be at considerably greater risk of T2DM development [60]. Experts have also explored the association between the quantity of smoking and the incidence of T2DM. Heavy cigarette smoking, that is, the consumption of more than 20 cigarettes per day, has been shown to significantly increase the risk of T2DM development [60].

Radzeviciene and Ostrauskas [61] found out that people who smoke have twice the risk of developing T2DM compared to non-smokers. In a prospective study, Luo et al. [62] found out current postmenopausal women smokers had a significantly heightened risk of diabetes. Similarly, Wang et al. [63] conducted a meta-analysis of prospective cohort studies and found out the passive smoking was significantly associated with increase in T2DM risk. Even though smoking can decrease body weight, it is linked to central obesity; a major risk factor for T2DM. Smoking also thought to increase oxidative stress and inflammation, impair endothelial function, and directly damage beta-cells. The precise mechanism through which smoking increases diabetes risk and impairs glucose hemostasis is not clear, but existing evidence proposes that smoking increases insulin resistance [63].

Increased insulin resistance has been demonstrated in healthy young men who smoke. Smoking has also been shown to decrease insulin mediated glucose uptake by approximately 10% to 40% in smoking men compared to men who do not smoke [64]. Smoking has been linked to dyslipidemia prone to atherosclerosis. Smokers have been found to have lower levels of high density lipoprotein cholesterol and higher fasting

triglycerides, and increased small dense low density lipoprotein particle proportion. With regard to glucose homeostasis, smoking adversely affects glucose control [18]. Cigarette smoking has been positively correlated in a dose dependent manner to increased HbA1 following adjustment for potential confounding by dietary variables [64]. In addition, C-reactive protein is thought to play a role in mediating the process by which cigarette smoking increases the risk of T2DM [60].

For former smokers, low cumulative exposure to smoking and years since smoking cessation have been inversely linked to the risk of diabetes, with diabetes risk decreasing among non-smokers and after 10 years of quitting smoking. For former smokers with low cumulative prior exposure, increased diabetes risk is likely to dissipate soon after smoking cessation [62]. New quitters have been found to at a higher risk of diabetes particularly the heavy smokers. Weight gain also appears to increase the risk of diabetes among smokers. The elevated risk of diabetes has been found to remain higher among non-smokers even after adjustment for weight gain. These findings are suggestive that weight again and residual effects of smoking play a role in increasing the risk of diabetes among smokers [62]. Apart from increasing the risk of T2DM development, cigarette smoking is also acknowledged as a strong risk factor to complications and mortality in patients who already have T2DM. Smoking has been shown to increase the risk of nephropathy, cardiovascular disease, stroke, retinopathy, and neuropathy [64].

2.4.6 Alcohol Abuse

There is increasing consensus that consumption of alcohol is an influencing factor in the development of T2DM. The biological mechanism is not clear, but several factors

are thought to explain the association, including changes in alcohol metabolite levels, increased insulin sensitivity following moderate consumption of alcohol, increased concentrations of high density lipoprotein cholesterol, and the anti-inflammatory effects of alcohol [65]. The precise nature of the dose-response is unknown. In general, the association between consumption of alcohol and T2DM remains controversial. Some reviews have demonstrated that the relationship between alcohol consumption and T2DM is U-shaped, showing a decreased T2DM risk with moderate consumption of alcohol compared with both excessive drinking and abstaining [66].

While some researchers propose no relationship between alcohol consumption and T2DM, others have demonstrated that heavy drinking can increase hyperglycemia or T2DM risk [65], and still others continue to question the effects of excessive alcohol consumption on T2DM. For instance, Li et al. [65] did not find any association between consumption of more than 50g of alcohol per day and T2DM. Moderate consumption of alcohol has been associated with protective effects for T2DM in men and women. Some authors report that moderate alcohol consumption is linked to a 30% lower risk of diabetes in women and men [66]. The mechanisms of this protective effect of alcohol are attributed to that fact that moderate consumption of alcohol increase high density lipoprotein cholesterol and insulin sensitivity [65]

2.4.7 Obesity

Obesity is one of the commonest independent risk factors for T2DM [12]. Obesity is a multifaceted disorder in which genetic susceptibility interacts with environmental exposures resulting in a heterogeneous phenotype [50]. Currently, it is acknowledged some

of the obesity phenotypes are linked to high risk of T2DM development. Strong evidence also shows that that there is wide metabolic risk heterogeneity for specific adiposity mainly associated with excessive adipose tissue location [51]. Accumulation of visceral tissue is a vital predictive factor of glucose, lipid or atherogenic disturbances. Conversely, adipose tissue location in the lower body part is not linked to heightened metabolic alterations [50]

T2DM risk has been shown to increase significantly with increasing body mass index (BMI) above 25 kg/m2. When compared with normal BMI (22 kg/m2), T2DM risk increases by 2-8-fold at BMI 25, 10-40-fold at BMI greater than 30, and more then 40-fold at BMI greater than 35 depending on gender, ethnicity/race, age, and distribution and duration of adiposity. For instance, a BMI of 30-35 has been shown to increase T2DM incidence by more than10-fold in men and more then 20-fold in women. Obesity is also thought to be a precursor for T2DM after insulin resistance [51]. Insulin resistance is among the earliest prediabetic state hallmarks and is a consequence of a multifaceted interplay between environmental factors that favor obesity such as excessive consumption of high-calorie foods and increased sedentary lifestyle coupled with a susceptible genetic background [3]. Obesity prevalence in the United States is greater among black and Hispanic ethnicities, and T2DM risk is likely to be greater in this group compared to obese individuals of European background [5]. Nonetheless, in individuals of south Asian background, obesity bestows a considerably higher T2DM risk, to the extent that a BMI of 27.5 kg/m2 is linked to similar morbidity to a BMI of 30 kg/m2 in people of European background, making some legislators to propose that a BMI of 22-23 kg/m2 should be regarded as overweight in people of south Asian background [51].

Even though excess fat is any part of the body is linked to increased T2DM risk, the generally agreement is that abdominal fat accumulation (central obesity), as evidenced by an increased waist: hip ration is an independent T2DM risk factor regardless of the degree of obesity. This is primarily ascribed to increased visceral (intra-abdominal) adiposity. Excessive lipid deposition in liver and muscle also increases T2DM risk through intracellular lipotoxicity mechanisms [51]. Central obesity increases visceral region mass effect with associate increase in free fatty acid mobilization from the individual visceral depot fat cells into the portal vein. These factors result in marked elevation of the levels of free fatty acids in obese persons leading to hyperglycemia, hepatic insulin resistance, and hyperinsulinemia. Additionally, even though the effect is likely to be less marked, increased subcutaneous fat in the upper body in obese individuals causes excess peripheral circulation free fatty acids resulting in the inhibition of insulin-mediated uptake of glucose in muscle potentially impairing pancreatic insulin secretion [50].

Lipotoxicity represents an important pathogenic association between obesity, insulin resistance, and T2DM. It describes the harmful cellular effects of fatty acid concentrations that are chronically elevated and lips that are excessively accumulated in tissues other than adipose tissue, acknowledging that excess adipose tissue usually causes heightened supply of fatty acid in obesity [7]. It is well acknowledged that excess adiposity promotes insulin resistance onset and severity, contributing to impaired glucose tolerance (IGT) and T2DM emergence and progression. In fact, approximately two-thirds to three-quarters of people who develop diabetes have a medical history of obesity, implicating excess chronic adiposity as the strongest T2DM risk factor [51].

The major pathway through which excess adiposity causes impairment in glucose metabolism is increased fatty acid supply into the circulation. Constant positive energy balanced is linked to increased triglyceride storage, resulting in expansion of adipose depots and increased fraction of hypertrophied adipocytes. Under normal insulin sensitivity, the hormone-sensitive lipase activity is suppressed by insulin resulting in reduce lipolysis and subsequent limitation of fatty acid supply into the circulation [17]. Conversely, enlarged adipocytes are less sensitive to the antilipolytic insulin action, resulting in increased fatty acid liberation and turnover. Muscle and liver can take up the fatty acids and used them in competition with glucose as energy source. Therefore, glucose-fatty acid cycle imbalance increases fatty acid availability and oxidation and reduce glucose utilization [5]. Additionally, there is production of fatty acid metabolites, which alter the intracellular insulin signaling post-receptor pathway and impair insulin-stimulated transport of glucose in muscle. Energy generated through oxidation of fatty acids can be used for hepatic gluconeogenesis. Fatty acid metabolites that impair the action of insulin are likely to inhibit the normal insulin suppression of gluconeogenesis. Therefore, the glucose-fatty acid cycle abnormalities make it possible for the increased fatty acids to worsen hyperglycemia and insulin resistance [51].

In insulin resistance, the adipocytes insensitivity to insulin leads to elevated free fatty acids, which is a typical feature of T2DM, and strongly linked to insulin resistance and β-cell dysfunction [15]. Therefore, it is becoming increasingly evident that reducing the levels of free fatty acids is a major goal in T2DM management. Prospective epidemiological studies have demonstrated that elevated levels of free fatty acids are a risk marker for long-term glucose intolerance and subsequent T2DM development [51].

Various hypotheses have been put across to explain the link between obesity and insulin resistance. One of them is the adipokine hypothesis, which holds that obesity causes an alteration in the profile of adipokines (adipose tissue secreted hormones). In obesity, adipose tissue is thought to secrete proportionally fewer adipokines that enhance insulin sensitivity and more that trigger insulin resistance [18]. The other hypothesis is the inflammation hypothesis, which holds that obesity increases chemokine secretion from adipocytes, which then trigger macrophage infiltration. Obesity is also thought to increase the activation of macrophages, which then produce cytokines with resultant insulin sensitivity [50].

2.4.8 Essential Hypertension

Hypertension, particularly systolic hypertension, is acknowledged as a strong independent modifiable risk factor for T2DM. Individuals with systolic hypertension have been shown to have a 4.6-fold likelihood of T2DM development compared to their normotensive counterparts [67]. It has been demonstrated that even though both diabetes and hypertension occur independently, they exacerbate each other. A greater percentage of patients have been found to develop hypertension following diabetes diagnosis (43.1 percent) relative to 23.1 percent of patients who had been diagnosed with hypertension before the diabetes diagnosis [68]. Isolated systolic hypertension has been shown to occur earlier in diabetic individuals than non-diabetics. The precise mechanism through which diabetes develops in hypertension has not yet been elucidated. It is thought that the association between hypertension and T2DM is complex and that it may involve various mechanisms [7].

Hypertension is thought to contribute to T2DM onset through the following pathways: (a) diminishing skeletal muscle slow-twitch fiber insulin sensitivity; (b) reducing glucose and insulin delivery by decreasing skeletal muscle blood flow; and (c) decreasing insulin postreceptor signaling through PI3K-Akt pathway. T2DM and hypertension share several of the same contributing biological and behavioral risk factor, including physical inactivity, high-dense-energy food, obesity, and adverse levels of C-reactive protein, IL-6, and TNF-a [68]. Metabolic syndrome, hyperlipidemia, and obesity are thought to explain the link between hypertension and increased T2DM incidence [69]. T2DM and hypertension are major components of the metabolic syndrome, usually co-exist, and result in a worsening in cardiovascular prognosis and increased burden than either condition individually [68]. Decreased baroreceptor sensitivity, subtle autonomic dysfunction, endothelial dysfunction secondary to hyperglycemia, and associated nephropathy are some of the mechanisms through which hypertension develops in diabetes [67].

2.4.9 Pure Hypercholesterolemia

Pure hypercholesterolemia or familial hypercholesterolemia is a genetic condition typified by very high levels of low-density lipoprotein (LDL) cholesterol (LDL-C) from the time of birth. It is associated with higher risk of myocardial infarction or mortality in early life, both of which can be delayed or prevented [70]. Pure hypercholesterolemia is inherited in an autosomal dominant manner and may be present in a heterozygous or homozygous form. It is a kind of autosomal dominant hypercholesterolemia (ADH). Familial hypercholesterolemia is among the commonest monogenetic disorders. Of the two

forms, heterozygous familial hypercholesterolemia is more common compared to the homozygous form. The long known classical familial hypercholesterolemia (ADH1) is defined gene *LDLR* mutations. This gene usually encodes for the LDL receptor (LDL-R). The subsequent defective receptors cause inhibition or decreased uptake of LDL-C into the cells. Currently, over 1,700 variants of the *LDLR* mutations have been identified worldwide [70]. Mutation in the APOB gene has also been shown to decrease the uptake of LDL-C. APOB gene encodes for apolipoprotein B (ApoB), the protein responsible for the recognition of LDL-C and enabling LDL-C binding to the LDL-R. The resultant condition is termed familial defective ApoB100 (FDB) or ADH2. Loss of function mutations lead to higher LDL-R expressions on cell surface and lower LDL-C levels. LDLR mutations are responsible for most cases of pure hypercholesterolemia, accounting for more than 95% of the cases. Mutations involving other genes are less common, with APOB mutations comprising of 2%-5% of the case and LDLRAP1 and PCSK9 mutations each comprising of 1% of all pure hypercholesterolemia cases [70]. A body of experimental and clinical evidence is in support of an association between LDL-C, atherosclerosis and inflammation. Accumulation of cholesterol in the artery initiates a local and systemic inflammatory reaction through multiple pathway activation, including adaptive and native immune responses [71].

Even though the precise mechanism is not clear, pure hypercholesterolemia is thought to contribute to T2DM by triggering chronic inflammation and insulin resistance. The insulin resistance that leads to T2DM development is often linked to the dyslipidemic triad increased triglycerides mainly present in very low-density lipoprotein remnants; decreased high-density lipoprotein cholesterol; and increased concentration of smaller,

denser low-density lipoprotein particles [72]. The pathophysiologic mechanism associated with dyslipidemia is the increased release of free fatty acids from insulin-resistant fat cells. The increased free fatty acid flux into the liver in the presence of adequate glycogen stores enhances the production of triglyceride with in turn triggers apolipoprotein B and VLDL cholesterol secretion. The impaired ability of insulin to block the release of free fatty acids results in heightened hepatic production of VLDL, which correlates the extent of fat accumulation in the liver [73].

The increased levels of triglycerides and VLDL cholesterol in plasma are associated with decreased HDL cholesterol levels and increased small dense LDL cholesterol concentration. The high triglyceride and low HDL cholesterol levels, and increase small dense LDL cholesterol have been shown to accelerate insulin resistance and increase the risk of T2DM development. These changes also increase the risk of complications, particularly cardiovascular disease development in patients who are already diabetic [72]. The disturbance in lipid metabolism seems to be an early event in T2DM development, potentially preceding the disease by many years. The various components of diabetic dyslipidemia, including plasma lipoprotein and lipid abnormalities, are thought to be linked metabolically. Triglyceride-rich lipoproteins after meals, apolipoprotein B 100, remnant lipoproteins, and small dense HDL particles have been found to be elevated in T2DM [73]

2.4.10 Pure Hyperglyceridemia

Hyperglyceridemia is a fasting plasma triglyceride measurement that is increase above the 95th percentile for sex and age, albeit additional qualitative or qualitative lipoprotein abnormalities have also been shown to be present. It is possible for patients to

fluctuate between hypertriglyceridemic states. In the presence of adequate metabolic stress, mild or moderate hypertriglyceridemia is likely to deteriorate into severe hypertriglyceridemia [74]. Increased concentrations of plasma triglycerides contribute to increased risk of cardiovascular disease, both directly and because these elevations contribute to metabolic syndrome, obesity, pro-thrombotic and pro-inflammatory biomarkers and T2DM. The prevalence of Hyperglyceridemia is as high as 50 percent in patients with T2DM and is usually unresponsive to statin treatment [75]. Plasma triglycerides come from two main sources: (1) endogenous (from the liver) and transported in very-low-density lipoprotein (VLDL) particles and (2) exogenous (from dietary fat) and transported in chylomicrons [74]. These chylomicrons and lipoproteins are hydrolyzed within muscle and fat tissue by lipoprotein lipase into free fatty acids. Following a meal, more than 90 percent of the circulating triglycerides originate in the intestines and become secreted in chylomicrons. The increased triglyceride-rich lipoproteins in plasma are a consequence of increase production from the intestine and liver [76].

Pure hypertriglyceridemia is linked to increased risk of insulin resistance, hypertension, diabetes, obesity, hyperuricemia, and cardiovascular disease [75]. Abnormalities in the metabolism of triglyceride-rich lipoprotein (TRL) are typical features of T2DM. Metabolic abnormalities resulting in hypertriglyceridemia include increased hepatic TRL secretion due to delayed TRL clearance and insulin resistance. This setting of hypertriglyceridemia is characteristic for T2DM. The increased triglyceride production could be attributed to excess FFA acids returning to the liver, especially in the context of insulin resistance and visceral obesity, and de novo production of triglycerides due to hyperinsulinemia. Increased levels of FFA are independent T2DM risk factors and can

trigger metabolic derangements in organs such as the pancreas and the liver. FFA overload, hypertriglyceridemia, and accumulation of lipids in non-adipose tissues influence both insulin secretion and insulin action, and often associated with T2DM development [76].

2.4.11 Vitamin D Deficiency

Nutritional deficiencies, and in particular vitamin D deficiency, have been associate with T2DM development [77]. Vitamin D is a fat-soluble nutrient obtained from dietary sources as cholecalciferol (D_3) or ergosterol (D_2). Production of D3 may also occur in the ski during exposure to ultraviolet rays [78]. Like T2DM, vitamin D deficiency is a major public health problem. It is estimated that it affects approximately 1 billion individuals [77]. Vitamin D deficiency may be a consequence of use of sunscreen, limited exposure to sunlight, prolonged wearing of covering clothes, low consumption of foods rich in ergocalciferol, age, and malabsorption syndrome [79]. It has been shown that the risk for vitamin D deficiency is substantial among African Americans and other ethnic groups with darker complexions. Elderly individuals also have a higher risk of vitamin D deficiency. Sunlight stimulates the production of D_3, thus limited sun exposure from pollution, sunscreen, and seasonal changes reduces its production. Melanin functions as a natural sunscreen and limits the production of vitamin D; hence, vitamin D deficiency in individuals with darker skin is common. Vitamin D intake is also affected by the high prevalence of lactose intolerance among African Americans [78].

Vitamin D receptors and the 1α-hydroxylase enzyme, which modulates the conversion of calcidiol [25-hydroxyvitamin D, 25(OH)D] to calcitriol [1,25-dihydroxyvitamin D, 1,25(OH)$_2$D$_3$] have been demonstrated in over 40 human cell types,

implying its likely role in the regulation of various metabolic processes. Recent data suggests that there is a potential association between levels of vitamin D and cardiometabolic diseases, including impaired glucose tolerance, obesity, arterial hypertension, T2DM, and atherogenic dyslipidemia. Even though the precise mechanisms are still not clear, deficiency of vitamin D is linked to increased risk of the above pathological conditions [79]. Increasing evidence shows that vitamin D is involved in various mechanisms in addition to bone metabolisms. Its role in deranged glucose metabolism and T2DM has been shown [77]. It is now well acknowledged that treating animals with induced T1DM using vitamin D slows diabetes progression. It has also been shown that high vitamin D doses in food consumed by risk-group children can reduce diabetes incidence. During assessment of carbohydrate metabolism, it was shown that lack of vitamin D was likely to cause greater levels of glycemia and increased risk of T2DM. There is an association between levels of 25(OH)D and responsiveness to insulin by tissues as well as between glycosylated hemoglobin and glucose levels in individuals without T2DM [79]

Insulin resistance and impaired insulin secretion are the hallmark defects that define T2DM. Deficiency of vitamin D is associated with impaired insulin synthesis and insulin secretion. Calcium is responsible for the regulation of insulin synthesis within pancreatic beta-cells, and insulin secretion. Vitamin D mediates calcium levels in plasma. Due to this mediation, some studies propose that deficiency of vitamin D is causal and that it precipitates impairments in the secretion of insulin in T2DM patients [78]. Recent studies show that vitamin D deficiency is likely to predispose to altered insulin secretion, glucose intolerance and T2DM. This can occur either directly through vitamin D receptor activation

or indirectly through calcemic hormones as well as through inflammation. Observational studies have demonstrated that increased vitamin D concentration is negatively associated with diabetes risk [79]. A recent systematic review showed that vitamin D consumption >500 international units per day was associated with decreased T2DM risk by 13% compared with vitamin intake < 200 international units per day. Persons with the highest 25OHD status (>25 ng/mL) were found to have a 43% lower risk of T2DM development compared with individuals in the lower group (<14 ng/mL) [80].

2.4.12 Asthma

Asthma is a chronic inflammatory lung disease that affects approximately 300 million people worldwide, and its prevalence continues to increase globally. Asthma is a major cause of morbidity and mortality [81]. It has also been acknowledged as a potential risk factor for the development of pro-inflammatory conditions, including T2DM [82]. Potential mechanisms for the hypothesized association between asthma and the increased T2DM risk include lung-related inflammatory cytokines and their effects on insulin sensitivity, genetic pleiotropy, adverse early-life exposures and their effects on development of organs, and direct hypoxia effects on glucose metabolism [81]. Respiratory bacterial and viral infections, pollutants, and tobacco smoking and important factors that induce a plethora of inflammatory pathways that is likely to mediate the association between asthma and comorbid diseases such as T2DM [81].

Low-grade inflammation reflected by the increase in levels of various pro-inflammatory biomarkers, including TNF-α, IL-6, adhesion molecules, and C-reactive protein has been acknowledged as a major contributor to T2DM development. It postulated

that increased circulating levels of some inflammatory cytokines as a consequence of chronic airway inflammation are also likely to contribute to insulin resistance development in the skeletal muscle, vascular endothelium, and liver, ultimately resulting in clinical expression of T2DM [82]. Studies have suggested that impairment in lung function is associated with increase prevalence of T2DM and metabolic syndrome, even after adjusting for adiposity. Some studies have demonstrated inverse associations between lung functions and insulin resistance or T2DM development in non-diabetic individuals in various populations [82].

Studies have explored the relationship between asthma and T2DM in adults, but the findings have been mixed. A Nurses' Health Study did not find any link between asthma and increased T2DM risk [83]. A Women's Health Study demonstrated a 1.5-fold increase in the risk of T2DM for asthmatic women, after adjusting for baseline BMI and other likely confounders [84]. Another population-based retrospective matched case-control study demonstrated more than two-fold increase in T2DM in patients with asthma compared with those without asthma. Nonetheless, the study did not adjust for important confounders such as smoking, adiposity, and other lifestyle factors [82]. Similarly, Mueller et al. [81] conducted a prospective cohort study to investigate the association between physician diagnosed child- and adult-diagnosed asthma and T2DM incidence in Chinese men and women. Their study demonstrated a positive relationship between self-reported, physician-diagnosed asthma and T2DM development risk that was modestly attenuated following adjustment for BMI [81].

2.5 Risk Factors for T2DM Complications

An interaction of social and economic factors may aggravate type 2 diabetes complications. According to a study, there is a significant correlation between type 2 diabetes complications and socio-demographic risk factors including age, race/ethnicity, type of insurance, the length of hospital stays, gender and patient's median household income and location. For example, black obese patients had the earliest onset of comorbidities compared to females of any other race [85]. In another study, socio-demographic factors were to found to be significant predictors of mortalities in individuals with diabetes compared to non-diabetic people. The socio-demographic factors included race, insurance, drugs, age, patient living conditions, income, and insurance. For example, age, number of diagnoses, drug risk mortality and comorbid conditions were significant risk factors for high mortality rates in diabetic patients as compared to non-diabetic individuals (P<0.05) [86].

2.5.1 Age

There seems to be relationship between age and the complications that occur in patients with T2DM. Previous studies have suggested that age is an important risk factor for diabetic complications. Older diabetic adults have been demonstrated to be at a higher risk for diabetes-associated complications [87].

Age is associated with the onset and progression of ketoacidosis. In a retrospective cohort study of patients with diabetic ketoacidosis (n=220) in Israel, the relationship between advanced age (≥65 years) and ketoacidosis was found to be significant; OR 11

95% CI (1.02-1.11) [88]. In addition, age is significantly associated with risk of nephropathy. In a cross-sectional randomized study of Saudi Arabia nationals with T2DM (n=54,670) aged ≥25 yearsto explore diabetic nephropathy and the associated risk factors, age was an important risk factor for diabetic nephropathy prevalence in these patients, varying from 3.7 percent in those age 25-44 years to 21.8 percent in those aged 65 years and older (P<0.0001). Patients aged above 45 years had an odds ratio of 2.16 (1.92-2.42) 95% CI of developing type 2 diabetes nephropathy [89].

According to a prospective cohort study of Chinese patients with T2DM (n=622) aged >60 years, the relationship between age and retinopathy in patients below 70 years of age is not significant (HR 1, 95%CI, P<0.01) but the relationship between age and retinopathy in patients above 70 years is significant, HR 1.36 (0.97-1.56), 95% CI, P<0.01 [90] The prospective cohort design enabled the researchers to ascertain a true causal relationship between advanced age and diabetic retinopathy. Similar finding has been supported by previous studies. For instance, in their cross-sectional study of Chinese patients with T2DM (n=523) aged 19-89 years, Zhang et al. [91] found a significant relationship between older age (>65 years) and diabetic retinopathy (OR=1.40 for every 10-year increase, P<0.0001). These findings were significant because the study was based on an adequate sample size (n=523), which implies that it was sufficiently powered to detect even small differences among the variables investigated. However, this study was limited by its cross-sectional design, which made it impossible for the researchers to evaluate causal associations [91].

Advanced age is also associated with type 2 diabetes peripheral neuropathy. A cross-sectional study of T2DM patients (n=294) aged 23-80 years in Bangladesh found that the relationship between age and neuropathy was significant in patients above 60 years old, OR 4.2, 95% CI (1.4-12.3) [92]. This significant finding was due to the adequate sample size used in the study (n=294). This study confirms previous reports concerning the relationship between neuropathy and advanced age. For instance, a previous case-control study of patients with T2DM (n=110) in Iran aged 20-80 years found a significant relationship between advanced age (>65 years) and diabetic neuropathy (P=0.04) in T2DM patients [93]. The case-control study design for this study made it possible for the researchers to establish a true causal association between advanced age and neuropathy [93].

Advanced age has also been associated with increased stroke risk in T2DM patients. In their four-year follow-up study of patients with T2DM (N=14,432; 7218 women and 7214 men) aged 40 to 97 years in Italy, Giorda et al. [94] found that the age-standardised stroke incidence (per 1000 person-years) was 6.3 in women (95% CI, 4.5-8.2) and 5.5 in men (95% CI, 4.2-6.8). Moreover, in a cohort study of patients with T2DM (1,479) and aged ≥61 years, age was significantly associated with peripheral circulatory disorders and was increasingly high in older patients (p<005). The HR for developing peripheral arterial disease was 1.32, 95% CI 1.17-1 [95]. Furthermore, multiple empirical studies on peripheral arterial disease [96, 97] confirmed that age is associated with peripheral disorders, which demonstrates a universally true relationship across all populations and groups. However, there was no evidence that age was an independent risk factor in the development or progression of hyperosmolarity syndrome [95, 98].

Furthermore, age is a significant risk factor for the development of T2DM renal complications. Thus, researchers found that age, among other risk factors including female sex, previous sensory neuropathy, decreased waist circumference, and increased insulin sensitivity, was a significant risk factor for developing diabetes-associated renal complications. More specifically, in univariate models, age at diagnosis (HR 2.07), among other factors, was associated with a high risk of development of reduced creatinine clearance (P < 0.01). In multivariate models, age at diagnosis (HR 2.15) was found to be independently associated with increased risk of having reduced creatinine clearance [99]. Similarly, a study found that baseline age, as well as baseline HbA1c, duration of diabetes, triglycerides, SBP, and the presence of retinopathy have significant association with the development of diabetic nephropathy, a dangerous renal complication [100]. In another study, researchers identified age and diabetes duration as significant risk factors having a strong impact on the development of diabetic nephropathy. Moreover, the authors added that such factors as socioeconomic background, gender, obesity, diet, and the high incidence of hypertension play an important role in the progression of diabetic nephropathy [101].

Popescu et al. [87] found significant positive correlation between diabetic neuropathy and higher age (65 years vs. 59 years; P=0.001). They also found age to influence diabetic neuropathy independent of other T2DM-associated risk factors. Research confirmed these results, as another study demonstrated that age was in the list of risk factors for developing T2DM neuropathy (age P < 0.001, dyslipidemia P = 0.03, glycated hemoglobin P < 0.001, duration of diabetes P < 0.001, etc.) [102]. Similarly, a study found that the prevalence of diabetic peripheral neuropathy (DPN) increased with

age (from 11.1% in the 23-40-year-old individuals to 32.3% in those aged 60-80). In this study, age > 60 years (OR 4.2, 95% CI 1.4 – 12.3) was one of the independent, statistically significant risk factors for the development of DPN [103]. Conversely, Nehring et al. [104] conducted a cross-sectional case control study to compare the risk factors of diabetic foot in T2DM patients (n=438) and diabetes risk factors in healthy subjects (n=462) age 58-72 years in Poland and found that diabetic foot risk decreased with the age of the patient (OR=0.94; 95 percent CI: 0.092 to 0.96; P=0.00001). While this study was sufficiently powered, given the large sample size, its cross-sectional design makes it impossible to establish a true causal association between ages and diabetic foot.

The significant association between advanced age and the various diabetic complications in patients with T2DM could be attributed to various mechanisms. One potential mechanism is that aging causes epigenetic changes that influence the expression of genes, resulting in impaired insulin secretion and persistent hyperglycemia. In addition, advancing age has been linked to poor glycemic control and prolonged duration of diabetes, which are thought to contribute to the increased incidence of complications [105].

2.5.2 Gender

Gender is about being male or female. It is a social construct that transforms a male in man and female in woman. Gender influences risk factors, causes, clinical features, therapeutics, prognosis and outcomes of various disease processes. Gender variations in diabetes may arise due to sexual hormones and genetic factors [26]. Research suggests that gender is a potential risk factor for diabetic complications in patients with T2DM.

Gender is associated with the development of type 2 diabetes ketoacidosis. A multicenter randomized study of T1DM (n=5615) and T2DM (n=1425) youths aged 0-19 years in the United States found a significant link between the male gender and ketoacidosis (P=0.01). The strengths of this study included its large sample size (N=7040), the population-based design, and the consistent ketoacidosis definition over time. The study shows a true causal relationship between male gender and diabetic ketoacidosis [26]. This connection is also supported in several more studies [106, 107].

Gender is also implicated as a predictor of nephropathy. In a cross-sectional randomized study, the relationship between nephropathy and the male gender was found to be significant with an OR 1.20 (1.14-1.27) 95% CI. These finding were significant given that the study was based on a very large sample size (n=54,670), making it sufficiently powered to detect any differences among the variables investigated [89]. Additionally, gender is associated with hyperosmolarity. According to study of diabetic patients, hyperosmolarity is much more common in women than in men [108]. However, previous studies do not confirm these results. Thus, for example, researchers found that female gender as a risk factor was non-significant for hyperglycemic hyperosmolar syndrome [109]. Furthermore, gender seems to influence ophthalmic manifestations in T2DM patients. In a study of patients with T2DM (64 women and 56 men0 aged 42-89 years in Greece, the male gender was associated with the presence of type 2 diabetes retinopathy and the relationship between gender, and T2DM retinopathy is significant, with an OR of 3.57 (1.67-7.62), 95%; P=0.001 [110]. Conversely, a cross-sectional study of Chinese T2DM patients (n=523) found a significant correlation between female gender and higher risk of proliferative diabetic retinopathy (OR=1.59, P=0.01). However, this finding may

have been influenced by the fact that diabetic retinopathy was determined from clinical examination using ophthalmoscopy instead of the standard fundus photograph grading. Evidence has shown that diabetic retinopathy status may be misclassified by ophthalmoscopy. Therefore, this finding should be translated with caution [91].

Gender is also associated with type 2 diabetes neuropathy. A retrospective study of patients with T2DM (n=830) in Pakistan found that the relationship between male gender and type 2 diabetes neuropathy is significant, OR 1.4, 95% CI (1.01-1.9) [111]. Al-Rubeaan et al. [89] showed that male gender was a significant risk factor for diabetic nephropathy with an OR (95% CI) of 1.2 (1.14 TO 1.27). These findings support previous studies that have shown a relationship between male gender and diabetic neuropathy. For instance, Booya et al. [93] found that the male gender was significantly associated with increased risk of diabetic neuropathy than the female gender (OR male/female 2.9; P=0.04). Similarly, Nehring et al. [104] found that male gender was significantly correlated with increased risk of diabetic foot in T2DM patients (OR=2.83; 95 percent CI: 1.86 to 4.28; P=0.00001). On the other hand, in descriptive study, sex was significantly associated with peripheral arterial diseases. More females than males (HR 1.27, 95% CI; 1.10-1.92) were found to be at risk. However, this study was mainly descriptive and these findings should be confirmed by well-designed randomized controlled trials [108].

The mechanisms behind the gender variations in T2DM complications is unclear but can be explained by the fact that female and male patients with diabetes differ in regard to behavioural, social and biological factors. Gender differences in compliance to diabetes treatment and diet as well body mass index may contribute to this variation in risk of

T2DM-associate complications. In addition, some authors have argued that these differences can be explained by variation in complication risk profiles and treatment intensity as well as by hormonal differences between males and females [54].

2.5.3 Race

Race seems to affect the development of various T2DM-associated complications. The association between age and these complications is complex and seems to be compounded by additional factors such as culture, income level, medication adherence, body weight, age, genetics, and dietary habits [57].

Race is associated with type 2 diabetes ketoacidosis. A multicenter study in the United States associated minority races or ethnicity (Blacks and Hispanics) with ketoacidosis prevalence p=019 [26]. Race is also associated with type 2 diabetes hyperosmolarity. According to a review, Blacks, Native Americans and Asians are at high risk of hyperosmolarity syndrome [112]. Similarly, African American race was found to be associated with increased risk of HHS [113]. In another study, however, researchers doubted whether hyperosmolarity occurs more often in African-American patients. Their findings revealed that there are no racial differences in susceptibility to this diabetes-related complication. More importantly, authors found that social background rather than race predisposes patients to develop hyperosmolarity, as ten out of 13 patients included in the study were socially isolated [114]. However, because the study was conducted 34 years ago and included a small sample size, its results are not reliable enough.

In addition, in a cohort study, race was significantly associated with peripheral arterial diseases. Black people had higher chances of developing the disease compared with non-black people (HR, 1.26; 95% CI, 1.01-1.93) [115].

Furthermore, a cohort study of T2DM patients in the United States found that racial/ethnic minorities had increased rates of diabetic kidney disease as compared to non-Hispanic Whites. In the study, Chinese, Filipinos, Hispanics and Non-Hispanic Black women had significantly higher odds ratio of developing proteinuric diabetic kidney disease compared to non-Hispanic Whites (P<0.01) [116]. A prospective study of T2DM patients (n=5,102) in the United Kingdom found the association between diabetic nephropathy and Indian-Asian ethnicity to be significant with a Hazard Ratio (HR) of 1.60 (1.26-2.06), P< 0.001, 95% CI [117].

This is in line with the study, which found that diabetic end-stage renal disease (ESRD) was more widespread in African Americans (1.9, 1.9–2.0), Asians (1.8, 1.5–2.1), Hispanics (1.4, 1.3–1.4), and Native Americans (1.9, 1.5–2.3) [118]. Moreover, researchers revealed that Native Americans (1.5, 1.1–2.1) and African Americans (OR=1.3, 95% CI 1.2–1.4) were more predisposed to developing early diabetic nephropathy than Caucasians. Researchers used large sample size (429,918 patients), which allows suggesting that these results are reliable [118]. Another study revealed the similar tendency towards the uneven prevalence of renal complications among representatives of different races. Thus, authors found that the incidence of ESRD was much higher among individuals of the African-Caribbean and Indo-Asian origin if compared to Caucasians [119].

In addition, race is associated with prevalence of diabetic retinopathy. The relationship between race and prevalence of retinopathy is statistically significant with the prevalence of any lesions of retinopathy being 46% higher in non-Hispanic blacks (P=0.07) and 84% higher in Mexican Americans (P <0.01) than in non-Hispanic whites. For non-Hispanic blacks, their higher risk factor level for retinopathy is thought to contribute to this difference, but there is no clear explanation for the difference observed in Mexican Americans [120]. These results have been confirmed in a study, which argued that Alaska Natives and American Indians, African Americans, Hispanics, Asian Americans, Native Hawaiians, and other Pacific Islanders have a higher prevalence of diabetes and its related ophthalmic complications compared to whites [121]. Similarly, other authors found that Non-Hispanic black individuals had a higher prevalence of ophthalmic manifestations than had non-Hispanic white individuals (38.8%; 95% CI, 31.9%-46.1%; vs. 26.4%; 95% CI, 21.4%-32.2%; P = .01) [122]. A comparative study of Asians versus American and Europeans showed that at diagnosis, Asians had considerably more background retinopathy proliferative retinopathy included (3.6 percent versus 1.6 percent). Contrary to this data, researchers found that race was not associated with diabetic retinopathy (DR) in a multi-ethnic Asian population (Chinese, Malays, and Indians) [123]. Lastly, the study also showed that Americans and Asians had considerably higher macroalbuminuria and microalbuminuria prevalence, albeit the two groups had similar levels of serum creatinine. In addition, the study found that patients of American race had more neuropathy, albeit the finding was not statistically significant [124]. Race was also found to be significantly associated with PVD in any ethnic groups (Native American-12.0%, Black-8.6%, White-7.4%, Hispanic-4.4%, Asian-4.3%, other-7.4%, P<0.0001) [125].

2.5.4 Family History of Diabetes

Family history is a known risk factor for development of diabetes. It also seems to have a role in influencing the development of T2DM-associated complications. Existing evidence indicate that genetic factors could play a role in microvascular and macrovascular diabetes-associated complications [124].

Severe retinopathy risk has been found to be four-fold higher in retinopathy-positive patients' relatives compared to those without retinopathy, implying that familial history of diabetes could play a role. Kuo et al. [126] approximated diabetic retinopathy heritability to range from 18 to 27 percent for general diabetic retinopathy, and from 25 to 52 percent for proliferative diabetic retinopathy in T2DM. Diabetic nephropathy heritability is thought to be higher compared to diabetic retinopathy, with reports of a range from 0.3 to 0.75 in various investigations [127]. In addition, family history of diabetes was found to be associated with ketoacidosis. For example, according to a study, family history, and HLA-associated high-risk genotypes specifically, are associated with an increased chance of presenting diabetic ketoacidosis. However, one needs to stress that the data on the association between ketoacidosis and family history is largely limited to type 1 diabetes, while information on type 2 diabetes is scarce [128].

Langefeld et al. [129], in a study of Caucasian patients with T2DM (n=662), found out that GFR and albuminuria heritability in T2DM was 0.75 and 0.46 respectively, following adjusting for covariates such as HbA1c and blood pressure. Earlier research regarding genetic factors for renal complications in T2DM centred on albuminuria as the main phenotype. Studies have identified various regions linked to diabetic nephropathy

inT2DM such as 18q, 10q, 9, 7q, 7p, and 3q chromosomal regions. A family investigation cohort study on diabetes and nephropathy of predominantly T2DM patients from all ethnic groups in the United States found that 11p, 7q, 7p and 6p chromosomal linkage regions contributed to diabetic nephropathy [130]. Various candidate gene studies for diabetic nephropathy have been conducted and have identified various genetic variants indicative of the link with kidney complications. Variants near KCNQ1 have been linked to diabetic nephropathy [127]. Janssen et al. [131] identified a repeat of trinucelotide in CNDP1 gene exon 2 to be linked to nephropathy in T2DM patients (OR 2.56. 95% CI 1.36-4.84).

Al-Rubeaan et al. [89] found a significant association between family history of diabetes and nephropathic, macroalbuminuria and microalbuminuria patients (P<0.0001) However, they found no significant association between family history of diabetes and ESRD (P=0.866). According to a prospective study, family history of diabetes is significantly associated with the onset and progression of type 2 diabetes retinopathy, with an HR of 1.19 (0.78-1.31); 95% CI; P<0.01) [90]. In another study, Kullo and Leeper argued that several risk factors for peripheral artery disease, such as dyslipidemia, type 2 diabetes mellitus, and hypertension, are heritable [132]. An observational study of patients with T2DM patients (n=2630) in India found no significant association between positive family history of diabetes and nephropathy in T2DM [100].

Additionally, according to a cohort study of patients with T1DM (n=510) aged <17 years, family history of diabetes is a significant predictor of hyperosmolarity syndrome in diabetes type 2 [128]. A critical case review revealed that, among those patients in whom family history was documented, nearly 85% with hyperosmolarity had a positive family

history of diabetes [134]. Moreover, as noted by other scholars, ketoacidosis and hyperosmolarity are often connected, developing in patients with obesity and a strong history of diabetes, among other factors [135]. Moreover, it has been found that pediatric patients with HHS share common features, as the majority of them are obese African-American males with a family history of T2DM [136]. As seen, this study related hyperosmolarity to a set of risk factors, not family history exclusively.

Another reviewed study found no significant relationship between family history and ketoacidosis in patients with type 2 diabetes mellitus. There was no evidence that family history of diabetes is an independent risk factor in the development or progression of neuropathy. These mixed results are attributed to the different study designs used in the studies and the differences in primary outcome measures in each study. However, there is convincing evidence that the HLA-linked high-risk genotypes are associated with higher risk for diabetes-related complications, including diabetic ketoacidosis [128].

2.5.5 Obesity

Obesity is a major global epidemic. It is defined by a body mass index (BMI) of ≥ 30 kg/m2. Obesity accompanying T2DM has been closely associated with increased activity of the sympathetic nervous system and insulin resistance. Obesity has been linked to increased risk of renal complications in patients with T2DM. It is believed that obesity increases the risk of renal complications in patients with T2DM through insulin resistance and increased sympathetic nerve activity [137]. Wijesuriya et al. [138] conducted a retrospective analytic study of T2DM patients (n=12,517) in Sri Lanka and found a significant relationship between nephropathy and high BMI (OR: 1.20; 95% CI: 1.11 to

66

1.29. Al-Rubeaan et al. [89] found that obesity had significant differences in patients with nephropathy relatively to those without nephropathy. They found higher percentage of microalbuminuria (54.4 percent) and macroalbuminuria (20 percent) in obese and severely obese patients. The prevalence of ESRD was also high (35.7 percent) in obese and severely obese patients. This finding is true across many different population groups, which is demonstrated in several other studies [139, 140, 141].

Obesity is also associated with hyperosmolarity in patients with diabetes type 2. According to a review study, obesity is associated with a significant risk of hyperosmolarity in diabetes type 2 [113]. In addition, obesity is associated with the onset and progression of type 2 diabetes retinopathy and the relationship between obesity and retinopathy is significant. A prospective study found that patients with a BMI of less than 25 (normal), had an HR of 1(no significant relationship), overweight patients (BMI 25-27.4) had an HR of 1.08 (0.88-1.32) P=0.26 while obese patients (BMI >27.4) had an HR of 1.19 (1.08-1.24); 95%CI, P=0.03 [90]. Similarly, obesity is associated with type 2 diabetes neuropathy. According Al-Kaabi et al, who conducted to a prospective cross-sectional study of patients with T2DM (n=394) in the United Arab Emirates, the relationship between obesity and neuropathy is significant, with an odds ratio of 1.06, 95% (1.00-1.11) [142]. A study supported this data, but research found no connection between obesity and DPN in the Asian population, which allows suggesting that obesity as a risk factor may be related to race [92]. Lastly, in a cohort study, baseline BMI was a significant risk factor of PAD-related outcomes. The HR was 1.01, 95% CI; 0.99-1.04 [98].

In another study, Nehring et al. [28] found a significant relationship between waist circumference 9or=1.028; 95 percent CI: 1.007 to 1.050; P=0.006), height (OR=1.08; 95 percent CI: 1.05 to 1.11; P=0.00001), and weight (OR=1.04; 95 percent CI; 1.03 to 1.06; P=0.00001), and increased risk of diabetic foot. Smith and Singleton supported these findings, arguing that obesity and hyperlipidemia were significant risk factors for developing diabetic neuropathy [143]. However, Wijesuriya et al. [137] did not find a significant association between increased BMI and other T2DM-associated complications except for nephropathy. In a cross-sectional randomized study, obesity was found to confer significant protective risk for nephropathy (OR 0.81; 95% CI, 0.75-0.88) [89]. These mixed findings can be attributed to differences in the study designs used by the researchers and perhaps differences in sample size. Studies with small sample sizes are not sufficiently powered to detect any differences in study variables.

2.5.6 Alcohol Abuse

The relationship between alcohol consumption and T2DM is complex and controversial. While excessive alcohol consumption is thought to contribute to hyperlgycemia in T2DM, moderate alcohol consumption has been shown to have protective effects. Therefore, it is necessary to explore more research on the relationship between alcohol consumption and complications in patients with T2DM. Alcohol abuse has been cited as a predictor of complications in T2DM patients. Alcohol is a risk factor in the development of nephropathy in type 2 diabetes patients [119].

A hospital-based prospective study of T2DM patients (n=120) in Bangalore to investigate the risk factors of diabetic nephropathy found the association between alcohol

and T2DM nephropathy to be significant, with an OR of 3.75 [144]. Furthermore, the study revealed that excessive alcohol consumption can damage the pancreas, which reduces insulin secretion and leads to the development and onset of T2DM and such related complications as ketoacidosis [145]. According to the study, the situation is aggravated when a patient has pneumonia or urinary tract infections, which contribute to the decrease in insulin's activity. Using the case study of a patient with a complex condition of ketoacidosis, researchers showed that this condition is greatly affected by alcohol abuse [145]. In another study, Hockenhull et al. used data from 191 post-mortem cases to investigate risk factors contributing to the development of alcoholic ketoacidosis, diabetic ketoacidosis, and hyperosmolar hyperglycemic state [146]. Results showed that ketoacidosis was widespread in individuals with a history of alcohol abuse, mainly because of the large amounts of ethanol and malnutrition. Interestingly, however, researchers also found that sometimes, ketoacidosis can occur in unexpected cases, where there is no history of alcohol abuse [146].

Alcohol consumption is also associated with the development of type 2 diabetes retinopathy and deterioration of visual acuity. According to a cohort study of patients with T2DM (n=1239) conducted by Lee et al., the relationship between type 2 diabetes retinopathy and alcohol consumption is not significant but the relationship between alcohol consumption and high risk of deterioration of visual acuity (OR, 1.83; 95% CI 1.34-2.48; P <0.001) [147]. In addition, alcohol is associated with the development of type 2 diabetes neuropathy. A cross-sectional study of T2DM patients (n=586) in north India conducted by Bansal et al. found that the relationship between alcohol consumption and the development of diabetes-related neuropathies was significant (P<0.033) [148]. These

finding were supported by Baldacchino et al. [149] in their cross-sectional retrospective study of T2DM patients (n=120) aged 25 to 70 years in Malta, which found a significant correlation between alcohol abuse and neuropathy in T2DM patients (P=0.022). Also, in a cross-sectional study of T2DM patients (n=300) in Cairo, Egypt, conducted by Preeti et al., it was found that alcohol consumption was not significantly associated with peripheral arterial disease [150]. Lastly, alcohol intake was found to be one of many precipitating factors in the hyperosmolar hyperglycemic state [151], which points that alcohol consumption is a risk factor in the onset and progression of hyperosmolarity.

2.5.7 Hypertension

About 60 percent of T2DM patient have hypertension (blood pressure ≥140/90 mmHg), and the risk of hypertension in these patients is twice as high as that in non-diabetic individuals. In addition, hypertension seems to precede T2DM onset. In patients with T2DM, hypertension has been linked to higher risk of microvascular and macrovascular complications. Evidence has shown that a decrease in systolic hypertension by 10 mmHg can reduce diabetic complication development by up to 12 percent and mortality by 15 percent [69]. Hypertension seems to exacerbate microvascular and macrovascular complications in patients with T2DM [152].

Research has shown an association between hypertension and renal manifestations in T2DM patients. It was also found be linked with diabetes-associated peripheral circulatory disorders, with an abundant body of literature supporting this finding in different population groups [153, 154]. Moreover, this risk factor seems to be associated with ketoacidosis. A study by Deeter et al. examined the relationship between blood

70

pressure, dehydration, and ketoacidosis in pediatric diabetic patients and found that a majority of patients had hypertension, which might have aggravated their condition [155]. However, the majority of such studies focus on type 1 diabetes, whereas patients with T2DM have not been studied in relation to the connection between ketoacidosis and hypertension.

Hypertension has been linked to increased risk of incident nephropathy in T2DM. In a cross-sectional randomized study, hypertension was a significant risk factor in the development of type 2 diabetes nephropathy (OR 2.42; 95% CI 2.0-3.0) [89]. Similarly, Agarwal et al. [96], in their cross-sectional study of newly diagnosed T2DM patients (n=300) found a significant relationship between hypertension and incident nephropathy, which was found to be up to 66.67 percent at blood pressure greater than 160/100 mmHg. Hypertension has been shown to be a strong independent end-stage kidney disease risk factor, suggesting that control and preventive strategies of this complication should focus on the management and control of hypertension. In addition, hypertension has been associated with more rapid nephropathy progression and kidney failure in T2DM patients [152]. Wijesuriya et al. [138], in their retrospective analytical study of 12,517 patients with T2DM aged ≥20 years, found a strong significant association between nephropathy and diastolic hypertension (OR: 1.52, 95% CI: 1.40 to 1.65) and systolic hypertension (OR: 1.96; 95% CI: 1.41 to 1.65).

Hypertension is also associated with hyperosmolarity in type 2 diabetes. According to a review, hypertension is a significant risk factor in the development of hyperosmolarity syndrome in patients with diabetes type 2 [128]. In addition, hypertension is a risk factor

for the onset and progression of type 2 diabetes retinopathy and the relationship between the two is significant, with an OR of 4.49 (1.15-17.49), 95% CI; P=0.030 [99]. Wijesuriya et al. [138] found significant association between retinopathy and diastolic hypertension (OR: 1.66; 95% CI: 1.52 to 1.82) and systolic hypertension (OR: 2.00; 95% CI: 1.83 to 2.18). Similarly, they found a significant relationship between stroke and diastolic hypertension (OR: 1.56; 95% CI: 1.04 to 2.33) and systolic hypertension (OR: 2.77; 95% CI: 1.84 to 4.17) [138]. Similarly, Zhang et al. [91] found a significant relationship between hypertension and increased risk of diabetic retinopathy (OR=2.11, P<0.0001).

Moderate to severe hypertension is associated with type 2 diabetes neuropathy. In a prospective, cross-sectional study hypertension was associated with an increased risk for peripheral arterial disorders. The relationship between hypertension and PAD was significant with an OR=1.6, CI=1.0-2.6; p-value=0.041 [117]. Wijesuriya et al. [138] found a significant relationship between neuropathy and diastolic hypertension (OR: 1.45; 95% CI: 1.33 to 1.57) as well as systolic hypertension (OR: 2.01; 95% CI: 1.86 to 2.18). The findings of this study suggest that hypertension increases the risk of microvascular and macrovascular complications in T2DM patients, and that the prevention of these complications can be achieved through prompt diagnosis and treatment of hypertension. Similarly, Preeti et al. [150], in their cross sectional study of patients with T2DM (n=283) in Tamil, Nadu, found that there was a significant correlation between hypertension and neuropathy (P<0.001).

Hypertension is associated with neurological manifestations in T2DM. According to a cross-sectional study, the relationship between hypertension and peripheral neuropathy

was significant, with an OR of 10.2 (2.8-38.0), 95% CI [156]. These findings have been supported in several more studies [156, 157, 158]. However, in a case-control study, Booya et al. [93] did not find any significant relationship between hypertension and diabetic neuropathy. This could be attributed to the small sample size (n=110), which was not sufficiently powered to detect even small differences between the study groups. Therefore, longitudinal studies are necessary to confirm the findings of this cross-sectional study.

2.5.8 Hypercholesterolemia

Hypercholesterolemia refers toelevation of cholesterol levels in blood (equal to or above 200mg/dL). It has been citedas a risk factor for complications in T2DM. Researchers have explored the role of hypercholesterolemia in the development of T2DM-associated complications. Hypercholesterolemia is implicated in the progression of T2DM-associated nephropathy, with a study by Bamashmoos and Ganem demonstrating a positive association between hypercholesterolemia and the degree of albuminuria [160].

High total cholesterol level is associated with an increased risk of T2DM retinopathy. According to a prospective study, the relationship between high total cholesterol and type 2 diabetes retinopathy is significant, with an HR of 1.38 (1.17-1.68) 95% CI, $P<0.01$ [90]. On the other hand, high levels of high-density lipoprotein cholesterol (HDL-C) was found to serve a protective factor against diabetic nephropathy progression in T2DM patients, with an OR of 0.971, 95%CI (0.953-0.989). Conversely, higher variation in HDL-C was demonstrated to be linked to a higher risk of progression of diabetic nephropathy with a hazard ration of 1.177 (1.032 to 1.341); 95% CI. The risk of diabetic nephropathy development was lowest among patients with lower variability in

HDL-C and higher levels of HDL-C. These findings confirm the protective effects of HDL-C against T2DM-associated complications, particularly diabetic nephropathy, which was found by Chang [161].

In a cohort study of T2DM patients (n=11,140) from North American, Europe, Australasia and Asia, Morton et al. [162] found a significant association between low HDL-C and increased risk of nephropathy in T2DM patients (P=0.001), but no relationship between low HDL-C and retinopathy (P=0.9). The lack of significant association between low HDL-C and retinopathy in this study can be explained by kind of retinal events investigated given that laser photocoagulation was the major retinal end point. This is likely to have diluted any causal association between the variables, if at all such an association was present. Overall, these findings indicate the existence of variations in the pathophysiology between nephropathy and retinopathy. In another cross-sectional study of T2DM patients (n=1060), Wang et al. [163] found that high levels of low density lipoprotein cholesterol (LDL-C) was significantly associated with microalbuminuria (P<0.001). Levels of LDL-C ≥2.6 mmol/l were significantly more common among T2DM patients with microalbuminuria relative to those without microalbuminuria (72.3 percent vs. 46.3 percent for women; 62.1 percent vs. 36.5 percent for men, all P<0.001). Zhang et al. [91] found a marginal correlation between higher very low density lipoprotein cholesterol (VLDLC) and elevated risk of diabetic retinopathy (OR=1.27 for each mmol/l increase, P=0.08). In addition, they found a significant relationship between hyperlipidemia and increase diabetic retinopathy risk (OR=2.19, 95 percent confidence interval 1.09-4.38, P=0.03).

Other studies did not associate hypercholesterolemia with hyperosmolarity. According to a review, low HDL cholesterol levels are significant predictors for hyperosmolarity [112]. On the contrary, other studies found that high total cholesterol is implicated in the development of T2DM neuropathy. According to a cross-sectional study, the relationship between high total cholesterol levels and neuropathy is significant, with an OR of 1.18, 95% CI (0.88-1.58) [128]. Lastly, LDL and HDL cholesterol were associated with the risk of developing peripheral circulatory disorders. However, the relationship was not significant (HR 1.00, 95% CI; 0.97-1.04).

 In addition, hypercholesterolemia was not associated with onset or progression of diabetic ketoacidosis [95]. In another cross-sectional study of patients with T2DM, Yadav et al [164] found a significant relationship between hypercholesterolemia and peripheral neuropathy (P<0.05). It was found that hypercholesterolemia causes a decrease in conduction velocity of both posterior tibial nerve and sural nerve, resulting in diabetic neuropathy, which is worsened even further in the presence of poor glycemic control. Similarly, Nehring et al. [104] found a significant relationship between hyperlipidemia (OR=0.54; 95 percent CI: 0.36 to 0.81; P=0.01) and elevated diabetic foot risk. Additionally, a cross-sectional study conducted by Preeti et al. [150] on T2DM patients (n=283) found a significant relationship between dyslipidemia and neuropathy development (P<0.001). However, Booya et al. [93] found no significant correlation between cholesterol level and diabetic neuropathy.

2.5.9 Hyperglyceridemia

Hyperglyceridemia is linked to insulin resistance and is thought to play a role in diabetes-associated complications. Consequently, various researchers have attempted to investigate this relationship. Thus, for example, Han et al. found that omega-3 fatty acid (O3FA) supplementation for managing hypertriglyceridemia showed benefits of significantly reducing albuminuria and maintaining renal function, which highlights the connection between hypertriglyceridemia and nephropathy [133]. High levels of triglycerides are also implicated in ketoacidosis, which is supported by a variety of empirical studies published within the last decade. For instance, an abundant body of literature explores the case of diabetic ketoacidosis (DKA)-induced hypertriglyceridemia and its influence on pancreatitis development [165, 166]. Additionally, another study investigated the case of hypertriglyceridemia-induced pancreatitis that led to overt diabetic ketoacidosis in a 46-year-old male patient. Researchers found that in rare cases, severe hypertriglyceridemia cause acute pancreatitis, which may lead to acute pancreatic failure and overt diabetic ketoacidosis in individuals with no previous history of diabetes mellitus [167]. Furthermore, a study explored the case of a patient presented with hyperglycemia and ketonemia. Their investigation revealed that hypertriglyceridemia, diabetic ketoacidosis, and acute pancreatitis are closely associated with each other, which emphasizes the need to conduct more studies exploring this unusual triad [168].

Moreover, high levels of triglycerides (equal to or above 150mg/dL) are associated with increased risk of type 2 diabetes retinopathy. According to a prospective study, the relationship between high levels of triglycerides and type 2 diabetes retinopathy is

significant, with an HR of 1.11 (0.87-128) 95%CI, P=0.16). The findings of this study are significant because the study was based on a large sample size (n=622), which ensure that the sample was sufficiently powered to detect even small differences in the variables of interest. In addition, the cohort design of this study made it possible for the researchers to establish a true causal relationship between the hyperglyceridemia and retinopathy [90]. According to a review, high triglyceride levels are significant predictors of hyperosmolarity syndrome in patients with diabetes type 2 [112]. Additionally, high levels of triglycerides are implicated in the development of type 2 diabetes peripheral neuropathy. According to a cross-sectional study of T2DM patients (n=502) in Al Ain, Abu Dhabi, the relationship between high levels of triglycerides and neuropathy was found to be significant, with an OR of 1.13, 95% (0.88-1.45) [169]. This finding is similar with that of other studies that have shown a relationship between hyperglyceridemia and neuropathy. In a cohort study, triglycerides were associated with the risk of developing peripheral arterial disease. However, the relationship was not significant (HR 1.00, 95% CI, 0.99-1.01) [95]. Hyperosmolarity was also found to be associated with hyperglyceridemia, as Gosmanov et al. argued that hypertriglyceridemia is often present in hyperosmolar hyperglycemic syndrome (HHS) [170]. For now, however, there is a lack of empirical evidence that would support the study's finding.

2.5.10 Smoking

Smoking is a well-known modifiable major risk factor for T2DM development. Similarly, studies suggest that there is a link between smoking and renal complication development and progression in T2DM patients. Smoking is believed to contribute to

T2DM complications due to its role in promoting central obesity, endothelial dysfunction, oxidative stress and inflammation [160].

Smoking has been associated with increased risk of nephropathy and retinopathy in T2DM. Bamashmoos and Ganem, [160], in their cross-sectional study of T2DM patients found that patients with diabetic nephropathy were more often former smokers and current smokers than normoalbuminuric patients (21.9 percent vs. 33.9%). Smoking has been associated with insulin resistance and poor glycemic control, contributing to these complications [171]. In their prospective cohort study, Gunton et al. [171], in their prospective cohort study of former smokers (n=34) demonstrated that smoking cessation resulted in HbA1c improvement (P<0.0001). In another prospective four-year follow-up study, Giorda et al. [94] found that smoking was a predictor of neurological manifestations, particularly stroke. In their cross-sectional, randomized observational study, Al-Rubeaan et al. [89] found that smoking was more common in patients with nephropathy, at 10.9 percent (P=0.001) and at 13.9 percent for patients with ESRD (P=0.029), but not in macroalbuminuria or microalbuminuria patients. Their study showed that smoking was a significant risk factor for diabetic nephropathy in T2DM patients with an OR (95% CI) of 1.18 (1.08 to 1.30).

Smoking is not an independent risk factor in the development of ketoacidosis. However, smoking is associated with type 2 diabetes nephropathy. The association between smoking and type 2 diabetes nephropathy was found to be significant [160]. Similarly, smoking was associated with the development of type 2 diabetes retinopathy and particularly Diabetic Macular Edema (DME). A cohort study of T2DM patients (n=64,784)

from Germany and Australia found that the relationship between smoking and retinopathy was significant (P<0001) [172]. In addition, smoking was associated with type 2 diabetes peripheral neuropathy. According to a cross-sectional study, the relationship between smoking and type 2 diabetes peripheral neuropathy is statistically significant. In a cohort study, daily smoking was strongly associated with the risk for peripheral circulatory disorders. Quitting smoking was associated with a 30% reduction in related mortalities (p=0.001) [173]. This relationship is also confirmed in credible empirical studies [173, 174]. Conversely, Booya et al. [93], in their case control study, did not find any significant association between cigarette smoking and diabetic neuropathy. This finding could be attributed to the small sample size (n=110), which was not sufficiently powered to detect even small differences between the study groups. Therefore, well-designed studies with larger sample sizes are necessary to help confirm this finding. There seems to be no reliable data that could confirm the connection between smoking and hyperosmolarity. Existing research points to such precipitating causes of HHS as underlying infections, medication intake, substance abuse, undiagnosed diabetes, non-compliance, and coexisting disease, not mentioning smoking as a significant risk factor [151].

2.5.11 Vitamin D Deficiency

Vitamin D plays a critical role in cell antiproliferative and differentiation pathways. It is also involved in renin-angiotensin system modulation, insulin resistance, cardiomyocytes health, vascular function, and immunity. Consequently, vitamin D deficiency has been linked to various diseases, including T2DM. Vitamin D deficiency is also believed to play a role in propagating T2DM-associated complications [176].

The association between vitamin D deficiency and onset or progression of ketoacidosis has relatively been under-investigated, suggesting the need for further studies in this area by researchers. However, available studies show that the deficiency results in worse health outcomes for type 2 diabetes in general. Vitamin D Deficiency is implicated in the development of nephropathy in type 2 diabetes patients. According to a multicenter randomized controlled trial, the relationship between Vitamin D deficiency and progression of type 2 diabetes nephropathy (>50% increase in serum creatinine concentration, End Stage Renal Disease (ESRD) or death) is significant, HR 3.79, 95% CI, 1.20-12.02; P+0.02 [176]. Vitamin D Deficiency was also significantly associated with >50% increase in serum creatinine concentration or ESRD (HR, 2.88; 95% CI, 1.84 to 7.67; P=0.04) [176]. In addition, Vitamin D deficiency is closely associated with the development and progression of type 2 diabetes retinopathy in type 2 diabetes. In an observational case-control study, the relationship between Vitamin D deficiency and retinopathy was found to be statistically significant as patients with severe deficiency had an increased risk of retinopathy (Relative Risk, RR=1.43, P=0.03) [177].

Another study evaluated the association between low vitamin D levels and diabetic nephropathy across different racial/ethnic groups [178]. Researchers found that of 1216 adults with diabetes, 30.7% had nephropathy, 48.9% had vitamin D deficiency, and 36.6% had vitamin D insufficiency. Interestingly, ethnic minorities were found to be more predisposed to having nephropathy (Hispanics 38.5%; non-Hispanic blacks, 36.2%; non-Hispanic whites, 27.8%; P = .02) and vitamin D deficiency (non-Hispanic blacks, 80.4%; Hispanic, 59.0%; non-Hispanic whites, 39.5%; P < .01) [178]. Similarly, the recent study by Xiao et al. found that out of 240 patients with diabetic nephropathy and 60 healthy

controls involved in the study, Vitamin D levels were lower in the first group. As diabetic neuropathy progressed, Vitamin D levels gradually decreased, especially if compounded with such risk factors as obesity, age, glucose level, and impaired renal function [179]. Thus, empirical research provides evidence of a universally true relationship between Vitamin D deficiency and diabetes-associated renal complications.

Similarly, in a randomized controlled study, vitamin D deficiency was independently associated with type 2 diabetes neuropathy. The relationship between vitamin D and type 2 diabetes neuropathy was significant for male patients (p=0.005). Compared to male patients with vitamin D sufficient, insufficient males had an increased risk of type 2 diabetes neuropathy (OR, 7.69; 95% I, 1.52-20.05) [177]. Also, in an observational study by Jung et al., vitamin D deficiency was associated with the development of the peripheral vascular disease. For each 50nmol/L difference in baseline blood 25-hydroxyvitamin D concentration, the risk of incident cardiovascular events changed by 20% (95% CI P=0.01) [180]. There was no evidence that Vitamin D Deficiency was an independent risk factor in the onset or progression of hyperosmolarity syndrome. Anyanwu et al. [181] conducted a single-blind, prospective randomized placebo-controlled trial to investigate Vitamin D supplementation effect in T2DM patients. They found that Vitamin D supplementation was associated with significant glycemic control improvement. This finding suggests that Vitamin D can reduce the risk of complications in T2DM by improving glycemic control.

2.5.12 Asthma

The association between asthma and T2DM and its associated complications is intricate and needs further exploration because epidemiological data have shown mixed results. However, existing data suggest an association between asthma and increase insulin sensitivity, but further research is recommended to clarify the association [182]. In a cross-sectional analysis study of T1DM (n=1683) and T2DM (n=311), Black et al. [183] found an association between asthma and diabetic complications, especially patients with T1DM but not T2DM (P=0.34). However, a prospective cohort study of female nurses (n=103,614) found no significant relationship between asthma and development of neuropathy, Relative Risk (RR) 1.0 (0.8-1.2), 95% CI [84]. The connection between asthma and neurological complications is under investigated, with the majority of findings focusing on the association between lung function and T2DM, without paying attention to this type of complications, which points to the need to confirm the data in future empirical studies [184, 185]. There is no evidence that asthma is an independent risk factor of any other type 2 diabetes complications.

2.5.13 Hyperlipidemia

Hyperlipidemia is a condition characterized by high levels of lipids and cholesterol in the blood. Primary hyperlipidemia has genetic causes whereas secondary hyperlipidemia is as a result of underlying conditions including diabetes. It is common in patients with T2DM, occurring in approximately 50 percent of this population [186]. Hyperlipidemia is a significant risk factor for several complications of diabetes type 2. Al-Rubeaan et al. [89], in a cross-sectional randomized controlled study, found that hyperlipidemia was a

significant risk factor in the onset and progression of nephropathy in diabetes type 2, with an odds ratio of 1.57 (1.49-1.66, 95%). Another study conducted by Rosario found that hyperlipidemia is among the most significant risk factors for diabetic nephropathy in T2DM population [187].

A case-control study did not find any correlation between hyperlipidemia and neuropathy in type 2 diabetes [93]. In a cross-sectional study of Chinese patients with T2DM (n=500), hyperlipidemia was found to be a significant risk factor in the onset of diabetic retinopathy, with an odds ratio of 2.39, 95%CI (1.02-5.66) [91]. A study supported these findings in a cross-sectional observational study of 140 patients in Bangladesh. Researchers have found that those individuals having diabetic retinopathy had significantly higher levels of serum total cholesterol (272.33 mg/dl as compared to 187.70 mg/dl in patients without retinopathy and 185.92 mg/dl in non-diabetic participants) [188]. Similarly, authors examined diabetic patients aged 15-50 years in Sweden and found that hyperlipidemia is significantly associated with the development of diabetic retinopathy [189]. Thus, results show that the relationship is true across different population groups. Finally, a cross-sectional study of T2DM patients (n=110) with undertreatment of diabetes in India found that hyperlipidemia was significantly associated with peripheral arterial disease, with a relative risk of 1.763 [190]. However, there was no evidence that hyperlipidemia was an independent risk factor for the onset or progression of ketoacidosis and hyperosmolarity in type 2 diabetes mellitus [190]. This could be attributed to the observational design of the study.

2.6 Logistic regressions

Logistic regressions are test that are used to predict or model the effect of independent variables on a given dependent variable. Different types of logistic regression models exist and each models characterized by the nature of the response it handles. One of the models is the ordinal logistic regression model. The ordinal model is used to analyze for the ordered response such as good, bad or excellent. The models the fall under the ordinal logistic regression include mean response models and proportional odds models. The other type of logistic regression is the nominal logistic regression that is applied in the modeling of responses that have multiple levels but not ordered such as skin color. Examples of models under the nominal logistic regression model are the multinomial and generalized logit models. The other type of logistic regression is the binary logistic regression that is characterized by two-level dependent variable response. The generalized additive models, case-control models and Bradley-Terry models are examples of the binary logistic regression models [191].

A binary logistic regression is a regression expression that is defined by a binary categorical dependent variable. A binary categorical variable means is that the outcome of the variable can only take two possible outcomes [191] In an example where the survival of the patient is determined by two factors (independent variable): the number of encounter hours with the doctor and the age of the patient, the survival of the patient can be termed as the dependent variable. If the survival of the patient is recorded regarding surviving or not survive, then this dependent variable (patient survival) is termed as a binary categorical variable. The categorical variable in a binary logistic regression should be binary; should have only two options such as yes or no, true or false, survive or not survive [192]. The

binary categorical variable in binary logistic regression is normally assigned dummies such as 1,0. The independent variables can, however, be continuous; from the example given above, the number hours of an encounter with the doctor (x) and the age of the patient (n) are continuous independent variables [193].

The binary logistic regression gives estimation, in probability terms, that a dependent variable is present (patient survives) based on the values of the independent variable (x and n). The logistic regression is expressed using a standard equation below:

$\ln(p/(1-p)) = \beta_0 + \beta_1 x_1 + \beta_2 x_2$ where $\ln(p/(1-p))$ is the probability of the dependent variable being present, β_0 being the model constant, β_1 and β_{21} being the constant of the respective independent variable. The β_0, β_1, and β_2 are always given by the output of the model computation [194].

Based on the example used above, the number hours of an encounter with the Doctor (x_1) and the age of the patient (x_2) will give the probability that the patient will survive. The probability should be between 0 and 1.

2.6.1 The use of Binary Logistic Regressions in Classification

The binary logistic regression can be used for the purpose of classification of the outcome that is binary [195]. Considering another example where the status of cancer is to be determined as either malignant or benign, the models can be used to make a prediction on the status of cancer of the examine patient or population. In this example, the only expected outcome is either malignant or benign, therefore, binary and a dummy can be allocated.

To make classification using binary logistic regressions one should first formulate a hypothesis and then establish the decision criteria [196]. A hypothesis that is formulated

should be testable [197]. A simple decision criterion on the outcome is usually based on the closeness of the probability outcome of the model to 1 or 0. The decision criteria should also be based on valid statistical background [198]. The criteria that are used in binary logistic regressions is based on whether the probability outcome is ≥ 0.5 or <0.5. If the probability outcome is ≥ 0.5 it means that it is closer to 1 than it is to 0. Therefore, the hypothesis that dependent variable is present is accepted. However, if the probability outcome is <0.5, it indicates that the outcome is more close to 0. Therefore, the hypothesis that dependent variable is present is rejected199]].

Based on example 2 stated above, the classification of whether the cancer is malignant or benign using binary logistic regressions can be made based on the hypothesis that "The cancer is benign." The binary logistic regression model is then developed based on the different predictor variables. The binary logistic regressions equation that is obtained from the computed model is the used to establish the probability by substituting for the values of the predictor variable. The hypothesis that the cancer is benign is accepted if the value of the computed probability is ≥ 0.5. However, the hypothesis is rejected, and cancer classified as malignant if the computed probability is < 0.5.

The use of binary logistic regressions in classification is, however, limited in some scenarios. The fact that the model can only be used in cases where the dependent variable is categorical and contains only two mutually exclusive outcomes indicates that the approach cannot be used in classification problems with more than two possible outcomes [200]. The process of defining and coding the variables to be used in the binary logistic regressions analysis is a complicated process, which is time-consuming and requires thorough understanding and interpretation of the problem. The technique is, however,

superior to other classification approaches such as Chi-square and Fischer's exact test since the approach eliminates the influence of confounding factors that may result in erroneous conclusions.

2.6.2 Binary Logistic Regression for Prediction of Diabetes type2 with Complications

The prediction of type 2 diabetes with complication can be made using the binary logistic regressions by considering the effect of different predictor variables. The prediction of the type 2 diabetes with complication helps to simplify the classification of predicted diabetes in individuals. Simplification of diabetes by identifying the associated complication aids in the provision of personalized medication [201]. Martinsen et al. [202] used binary logistic regression to Predict type 2 diabetes and complications in Greenland in 2014 based on the 1993 and 1999 models. In their study, they made assumptions that the body mass index remained constant, and its trends continued to 2014. The binary regression model developed Martinsen et al. [202] was able to predict a 23% increase in the prevalence among women while the model predicted the presence of 50% of the cardiovascular complications in 2014.

Li et al. [203] carried out a study to assess the performance of logistic regression in predicting type 2 diabetes with peripheral neuropathy complication. The performance of the regression model was compared to the prediction model developed using multilayer perceptron. It was established that the area under the curve (AUC) for the regression model that was obtained was 0.8802 while the AUC for multilayer perceptron model was 0.8536. Based on the fact that the AUC of model is an indication of the specificity. The AUC of the logistic regression model was shown to be higher indicating that the model has higher specificity in predicting the occurrence of type 2 diabetes with neuropathy. The researchers

also indicated that the sensitivity of the logistic model was higher compared to the multilayer perceptron model.

Barski et al. [204] performed a binary logistic regression study to compare the presence of Diabetic Ketoacidosis in patients with type 2 and 1 diabetes. The finding of their study indicated that ketoacidosis complication was less prevalent in type 2 diabetes but the severity was high. The AUC for the regression model that was obtained was 0.9233 indicating high specificity. The risk factors that the model indicated to have high influence on the occurrence of ketoacidosis include age and diet. It was shown that older individuals have a higher risk of having the complication.

Grover et al. [205] developed a logistic regression to predict the occurrence of type 2 diabetes with diabetes nephropathy. Their models had 88.5% predictive power indicating high sensitivity. The models predicted that the older patients with history of high blood pressure and have a sedentary lifestyle have a higher chance of developing type 2 diabetes with nephropathy complications. Yoo and Park [206] performed a cross section to predict the risk type 2 diabetic retinopathy using logistic regression models. The researchers obtained prediction models with an sensitivity of 75.2% while the AUC was established to be 0.82% indicating high specificity. The researchers established that the patients with a higher likelihood of having diabetic retinopathy were older patients.

2.7 Artificial Neural Networks

2.7.1 Overview

Artificial neural networks (ANNs) are complex modelling techniques used to synthesize large volumes of information and give predictions through experiential learning [207]. They are developed from the concept of the functioning of biological neurons that carry

information, transfer it to other neurons in a complex network aiding physiological functions in the process. The superiority of ANNs over normative computer applications is their ability to analyze disorganized information and give results from incomplete data, due to their ability to learn on their own [208]. The use of ANNs has come in handy in the prediction of the incidence of Diabetes type 2, which would previously go up to ten years undetected due to insufficiency of pre-existing diagnostic methods. This type of diabetes accounts for 80-95% of the total cases of the diabetes, and is caused by the insufficiency of insulin secretion by the beta cells in the body, or resistance to insulin where the cells do not respond to secretions of the substance [209]. Complications such as Diabetic Ketoacidosis (DKA), nephropathy, retinopathy and neuropathy increase the mortality and morbidity of the disease and further necessitate better predictive models for detecting the disease in time for the increased efficiency of interventions [210]. This paper presents a summary of studies that explore the use of ANNs in detection of Diabetes type 2 with complications such as DKA, Nephropathy, Retinopathy, and neuropathy.

2.7.2 Artificial Neural Networks for Prediction of Diabetes type2

The induction of artificial neural networks in the diagnosis and forecast of type 2 diabetes has been well documented in research. Initial studies delineated the possibility of using ANNs as a classification method for both type 1 and type 2 diabetes [211]. Further research showed that the system was capable of 92% classification of diabetes type 2 and related complications. The discovery was important given that 22-50% of DT2M develop neuropathy within a short time, which was a major concern as it led to end-stage renal failure requiring transplant or dialysis that added an unsustainable fiscal burden to patients and possible fatalities [211]. However, the most specific study that investigated the use of

artificial neural networks in predicting type 2 diabetes with nephropathy was carried out on the Pima Indians and sought to establish the most susceptible group of patients to nephropathy and renal insufficiency [212]. Pima Indians are known to have high susceptibility to develop type 2 diabetes and related complications such as nephropathy. The study employed various statistical models with an aim of determining the best to use in the prediction of renal insufficiency and development of nephropathy among type 2 diabetes patients. The indicator used was the deterioration of the Glomerular Filtration Rate (GFR) in both cases [212]. The research showed that the actual GFR value was best determined using a tree-based model that had six-terminal nodes, but the identification of the group of patients who developed the complications of renal insufficiency and nephropathy was best done by Artificial neural networks [212]. This proved the superiority of the models in predicting DT2M with nephropathy.

Using ANNs in the prediction of diabetic retinopathy and ketoacidosis has also been established in research. Diabetic Retinopathy is retina damage that can lead to blindness as a result of type 2 diabetes [208]. The accumulation of glucose damages the blood vessels in the retina at the back of the eye leading to complications. One particular study sought to determine if the model could identify diabetic qualities contained within fundus images and further carry out comparison of the specificity and sensitivity with normative ophthalmologist screenings [213]. The study found out over 90% detection rates for vessels and exudates and 73% for hemorrhages. On comparison with ophthalmologist screening, 88% sensitivity and 83% specificity was determined [213]. This proved that ANNs are reliable predictors of diabetic retinopathy. Ketoacidosis is a complication that occurs after the body resorts to burning of fats for energy due to inability to break down glucose [214].

This leads to build up of ketones in the body which can poison the individual. The detection of DT2M with ketoacidosis was achieved using Particle Swarm Optimized Artificial Neural Networks [214]. This technique was found to be highly effective in detecting groups of patients who were likely to develop the complication among diabetic and pre-diabetic patients [215]. Another study suggested the use of recurrent neural networks (RNNs), such as those with long short-term memory units (LSTMs) in the prediction of DT2M with ketoacidosis [215].

Studies have also established the employment of ANNs in the forecasting of diabetic neuropathy (DT2M neuropathy). Research in this line was necessitated by the long periods that patients took without the detection of the onset of the complications with up to 50% of patients with the problem unaware [216]. DT2M neuropathy occurs when high levels of blood sugar damage nerves in the legs and feet. The disease causes lots of pain to the patients and can extend complications to the digestive system and cause numbness all over the body as well. Ordinary statistical models that use logistic regression and T-tests among other tools are inefficient in determining the onset of diabetic neuropathy, which increases the disease burden to fatal levels [216]. Artificial neural networks offer a better solution with studies finding over 90% sensitivity in predicting the onset of DT2M neuropathy in given groups of patients. The use of ANNs can be applied in a variety of unbalanced data, which can be analyzed by their self-learning components thus enabling the determination of neuropathy caused by Diabetes type 2 Mellitus [216]. A study found high reliability of using artificial neural networks in determining the sensitivity of periphery nerves in controlling diabetic neuropathy on the short course of glycemic control [217]. The discovery of the ability to use ANNs in predicting DT2M neuropathy acted as a major

breakthrough in reducing the time for determining the onset of the disease. However, the use of ANNs in this respect is a subject of continuing research, with the applications being relatively new and widespread use still at the formative stages.

CHAPTER III

III. METHODS

3.1. Overview

This study employs the data from secondary source so this chapter contains the source of the data, information and description of statistical procedure that is used for data cleaning, data modeling and extractions. This chapter discusses all the procedures that study employs to fulfill the objectives of the study.

3.2 Research Design:

In this study, datasets were obtained from the Nationwide Inpatient Sample (NIS), Diabetes type2 as principle diagnosed and ICD 9 codes for every related factor were extracted, stored and two files will be used Core and Severity for this study. The Codes are given in table 4.

3.3 Data Sources

3.3.1 Data Collection Procedures and Ethical Considerations

NIS Core datasets for 2007 to 2012 has been used for analysis in this study. This dataset obtained from the HCUP Central Distributor. The researcher has submitted the use

of agreement for Nationwide Database to: HCUP Central Distributer Social & Scientific

Systemic. Through the E-mail: HCUPDistributor@ahrq.gov.

Table 4: ICD-9-CM Diagnosis Codes

Disease / Procedure	ICD-9-CM diagnosis
Diabetes type2 with ketoacidosis	25010,25012
Diabetes type2 with hyperosmolarity	25020,25022
Diabetes type2 with renal manifestations	25040,25042
Diabetes type2 with ophthalmic manifestations	25050,25052
Diabetes type2 with neurological manifestations	25060,25062
Diabetes type2 with peripheral circulatory disorders	25070,25072
Family history of diabetes	V180
Obesity	2780, 27800, 27801, 27802, V8521, V8522, V8523, V8524, V8525, V8530, V8531, V8532, V8533, V8534, V8535, V8536, V8537, V8538, V8539, V854
Alcohol Abuse	2910 2911 2912 2913 2914 2915 2918 29181 29182 29189 2919 30300 30301 30302 30303 30390 30391 30392 30393 30500 30501 30502 30503 76071 9800 3575 4255 53530 53531 5710 5711 5712 5713
Essential hypertension	4011, 4019
Tobacco use disorder	3051
Vitamin D deficiency	2680, 2681, 2682, 2689
Pure hypercholesterolemia	2720
Pure hyperglyceridemia	2721
Asthma	49300,49301,49302,49310,49311,49312,49320,49321,49322, 49381,49382,49390,49391,49392
Hyperlipidemia	2724

3.3.2 The Nationwide Inpatient Sample (NIS)

The Nationwide Inpatient Sample (NIS) is the main sources of data for this study. The NIS is considered to be the largest database in the United States for all-payer inpatient health care. This study has utilized NIS data for the following years2007, 2008, 2009, 2010,2011 and 2012. With a total of 452,223 records as shown in Table 5. These records were selected for patient who diagnosed with Diabetes type2 with complications with age of 18 years and older. Approximately 24.5% of the data population has a diabetes type2 with complications.

Table 5: The distribution of NIS data by years

Year	Ketoaci dosis	Hyperosm olarity	Renal Manifestations	Ophthalmic Manifestations	Neurological Manifestations	Peripheral Circulatory Disorders
2007	1,092	494	15,425	2,786	2,0107	3,313
2008	1,559	715	19,759	3,828	28,627	4,000
2009	1,818	841	21,836	4,376	33,789	4,485
2010	2,142	1,128	25,130	5,127	38,822	5,207
2011	2,965	1,642	33,992	6,514	52,576	6,903
2012	3,360	1,658	32,141	6,035	51,511	6,520
Total	12,936	6,478	148,283	28,666	225,432	30,428

3.4. Statistical Analysis and Tools

For this study Statistical Package for the Social Sciences (SPSS 22 Premium) is used for all the descriptive as well as advance data analysis that is logistic regression and Artificial Neural Network (ANN). Further Microsoft Excel 2013 is used in order to obtain the pie charts and bar charts for data description and comparative analysis.

3.4.1. Descriptive Analysis

Descriptive statistics are used in data analysis. Descriptive statistics is used to analyze the basic structure of data. In the current study, it has been preferred because of its

many advantages. Firstly, it simplifies large chunks of data in a more sensible way as compared to other methods. Each descriptive statistic tends to reduce data into a simpler summary, thus, making the data much easier to understand and interpret. There are four main types of descriptive statistics, names, and measures of frequency, central tendency, dispersion, and measure of position. Each of these types further includes other subtypes. The current study predominately employs the various sub-types of descriptive statistics. For instance, the age of participates is computed using mean and standard deviation. The main advantage of using SD is that it shows the extent to which data is clustered around the mean. It also gives more accurate information about how the data is distributed. In addition, other variables that concern symptoms of diabetes type-11 are calculated in percentages. The main advantages of using percentages in data analysis are that it allows for comparison between variables. This is important in a research, as it enables the researcher to establish the underlying relationship between variables.

3.4.2. Prevalence Rate

In medical and health sciences prevalence rate is most widely used measure. Based on existing cases of the disease, prevalence rate measures how widespread the disease is in a population. A prevalence rate is calculated as the total number of cases of a disease existing in a population divided by the total population.

3.4.3. Logistic Regression

Logistic regression is a model used to describe data as well as to explain the underlying relationship between dependent and independent variables. Logic regression is most preferred when the dependent variables are dichotomous or binary in nature.

Dichotomous variable means that the outcome is discrete, for instance, as present vs. absent, success vs. failure, or low, medium or high. For dichotomous variable, logistic regression normally assumes that the dependent variable being referred to is a stochastic event. In that, the outcome variable is coded as "0" or "1". The codes are then placed in the "Dependent" box while all the other predictors are put in a "Covariates" box [218].

The current study employs the use of logistic regression. The study involves the analysis of dependent and independent variables. In the regression model applied to this study, diabetes type-II is the dependent variable. On the other hand, diabetes type-11 risk factors including gender, age, race, obesity, drug and substance abuse, Asthma, Hypertension, dyslipidemia, Hypercholesterolemia, family history, and Vitamin D deficiency are all independent variables. The choice of this logistic regression model is to identify the important variables that can help predict the recurrence and prevalence of diabetes type-II. In addition, the study applies odd ratios for each of the independent variable in an effort to measure the rate at which the diabetes risk factors will occur in comparison to the rate at which it will not occur. This is important, as it shall help in classifying the risk factors in terms of their criticality as well as in making decisions regarding which risk factors should be given the highest priority in the clinical management of diabetes type-II (Knowler et al., 2002).

The probability used to classify a subject into particular category is based on odds provided by [218]:

$$Log\ Odds = e^{\beta_0 + \beta_1 x_1 + \beta_2 x_2 + \cdots + \beta_i x_i}$$

Where x_i are the independent variable while β_i are the regression parameters. Now the probabilities for each subject is calculated as

$$\pi = \hat{p} = \frac{Odds}{1 + odds} = \frac{e^z}{1 + e^z} = \frac{1}{1 + e^{-z}}$$

For $z = \beta_0 + \beta_1 x_1 + \beta_2 x_2 + \cdots + \beta_i x_i$, where z is also called 'logit' function or log odds. The logistic regression models of classification will be designed and NDS datasets using version 22 of the SPSS computer software. Diabetes type-II is the dependent variable in the NDS dataset, diabetes type-II is the dependent variable are gender, age, body weight, lifestyle, and family history. The distribution in both dataset is set to binomial. While the "link function" is assigned to "logit".

In which,

$$X\beta = \log (\mu/1 - \mu)$$

where

$$\mu = 1/[1 + \exp (-X\beta)]$$

3.4.3.1. Stepwise Estimation:

Stepwise estimation is a commonly sequential approach. It involves addition or deletion of variables with the aim of achieving a set of criteria. The use of this approach is significant because it enables the research to determine the role played by each independent variable during analysis. Variables that contribute to the study, which are incidental left out are added while those that do not contribute to the outcome of the study are deleted. Stepwise estimation analysis has a number of advantages worth mentioning. One of its outstanding advantages is the ability to deal with large amounts of potential variables and to allow the user to select the best options among a list of variables. This is an important

attribute as much as the current study is concerned as it involves a variety of variables under study.

Another positive trait is that stepwise estimation analysis is faster than other automatic methods. As a result, less time is spent on data analysis process as compared to other model-selection methods. The use of stepwise estimation allows the user to monitor variables being removed or added during analysis. This is an important attribute because it provides the user with valuable information concerning the quality of the variables used [222]. The stepwise estimation analysis is created for NDS datasets in the current study using SPSS software. In the NDS, diabetes type-II is also an independent variable in the NDS dataset of the stepwise estimation model whereas gender, age, body weight, lifestyle, and family history are the independent variables.

3.4.4 Neural Network:

An Artificial Neural Network (ANN) is a model that resembles the functioning of the biological nervous systems similar to that of the brain and process information. The main element in the working of the model lies in the structure of the information processing system [224]. The model consists of various interconnected processing elements known as "neurons", which work together to address a particular default. ANN are used because of several advantages they present to a study [225]. For instance, they demonstrate a remarkable ability in deriving meaning from complicated data. This therefore aid in the understanding of highly structured and complex information. In addition, ANNs tend to have compelling adaptive learning. ANNs can easily learn and accomplish tasks after brief training or initial experience. They are also self-organizing, as they can create their representation of the information received. Another interesting advantage is that they can

perform real time operations, by allowing parallel computation processes. This advantage is significant because it speeds up the data analysis process. There are various forms of ANNs. However, the most commonly one, and which is applied in the current study is the multilayer perceptron (MLP).

3.4.4.1. Multilayer Perceptron (MLP)

Multilayer Perceptron is (MLP) is arguably the widely used type of ANNs today. The MLP is described as a "feed-forward", particular because of its working mechanism that involves integrating and interlinking up to two hidden layers. Essentially, it is a function of one or more predictors, also described as called inputs or independent variables, which tend to minimize the prediction error of another set of "target" variables known as called outputs. As noted by [225], predictors and targets can comprise of a mix of both categorical and scale variables.

3.4.4.2. Architecture of Multilayer Perceptron (MLP)

Structurally, MLP comprises a set of layers that are arranged chronically. It comprises of three distinct layers to include the input layer, hidden layer, and output layer. The input layer is the top layer while the output layer is found at the bottom. The hidden layer is sandwiched between the input and output layers. Each layer consists of array neurons [224]. There is constant and coherent communication and exchange of communication from one layer to another. Each layer receives input signal containing information, manipulates the received information, and passes it to the adjacent layer. Figure 3.1 below shows the perfect working mechanisms of MLP [224].

It is noteworthy that the glow of information between the three layers is continuous [223]. The section below discusses the structure, composing and the function mechanism of each layer.
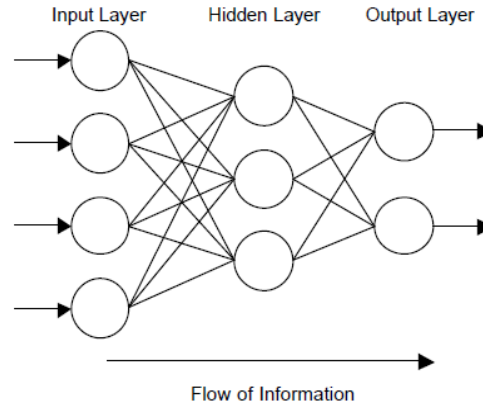
Figure 3: Multilayer Perceptron Feed Forward Network

3.4.4.3. Input Layer:

The input layer is the top outer layer of the MLP. It represented by a vector of predictor variable values $(x_1…x_p)$. As part of its working mechanism, this layer standardizes the predictor variable values in a range of "-1" to "1" [224]. It then distributes the values obtained to each of the receiving neurons in the hidden layer. It also has a constant input of "1.0", called the "bias", which is passed to each of the hidden layers. The bias is usual a product of a given weight, which is added to the sum going into the neuron [225].

3.4.4.4. Hidden Layer:

Once a neuron is realized from the input player, it gets to the hidden layer, where its value is multiplied by a given weight identified as (w_{ji}). The product is added together

101

producing a combined value (u_j). The weighted sum identified as (u_j) is then fed into a transfer function "σ" which outputs a value identified as (h_j). The output is then distributed to the adjacent output layer [225].

3.4.4.5. Output Layer:

One it exists the hidden layer, the neuron get into the output layer. Similar to what happens in the preceding layers, the neuron entering the output layer is multiplied by a weight (w_{kj}). The resulting weighted values are summed up together resulting in a combined value identified as (v_j). The weighted sum (v_j), is as well fed to a transfer function, σ, which outputs a value identified as (y_k).

Mathematically, a typical neural network is represented by the following equation [225].

$$y(k) = F \left(\Sigma \, wi \, (k) \cdot xi \, (k) + b \right)$$

$$i=1$$

Where:

- y(k) represents output value in discrete time (k)

- n represents the total of input variables

- F is a transfer function

- wi is weight value in discrete time (k), where i = from 0 to n

- xi is input value in discrete time (k), where i= from 0 to n

- b represents bias

Activation Function: In neural networks, activation function usually represents the rate potential action firing in the cell. The function is binary, in that, the neuron is either firing or not firing [223]. Usually, a line of positive slope is used to demonstrate the increase in

102

the rate of firing that occurs after an increase in current input. There are four sets types of activation function, which include identity, softmax, hyperbolic tangent, and sigmoid, all which are discussed below [219, 220]:

a) **Identity**

The formula of the identity function is : $\gamma(c) = c$. Essentially, the function takes real-valued arguments and returns them unaffected. When automatic architecture selection is used, this is the activation function for units in the output layer if there are any scale-dependent variables.

b) **Softmax**

The softmax function takes the form; $\gamma(c_k) = \exp(c_k)/\Sigma_j \exp(c_j)$. This function takes a vector of real-valued arguments and converts it to a vector, whose elements range between "0" to "1" and sum to 1. The function is only applies in conditions where all dependent variables are categorical.

c) **Hyperbolic tangent**

The hyperbolic tangent take the form: $\gamma(c) = \tanh(c) = (e^c - e^{-c})/(e^c + e^{-c})$. The function takes real-valued arguments and converts them to the range of "–1" to "1".

d) **Sigmoid**

The sigmoid function has the form: $\gamma(c) = 1/(1+e^{-c})$. This function takes real-valued arguments and converts them to the range of "–1" to "1".

The current study applies Neural Network classifiers for both NIS and NDS datasets using the SPSS analysis. Both datasets are "feed-forward" networks, implying that data only moves in one direction, which is from the input to the output neurons, via the hidden layers [223]. In the NIS dataset, diabetes type-II is a dependent variable in the

Neural Network model whereas age, race, obesity, physical activity, drug and substance abuse, hypertension, vitamin D deficiency, asthma, dyslipidemia, Hypercholesterolemia, and family history, are all independent variables. Likewise, diabetes type-II is also an independent variable in the NDS dataset of the Neural Network model whereas gender, age, body weight, lifestyle, and family history are the independent variables.

3.5. Measures to Compare the Multiple Regression and Multilayer Perceptron:

Since logistic regression and ANN are both classification models, it is important to establish the underlying similarities and differences. In light of the current study, two model: confusion matrix results and ROC curve were used to compare the two models.

3.5.1. Confusion Matrix Results:

The Confusion Matrix displays a classification table for each of the categorical dependent variable. Each table gives the number of cases classified for each dependent variable category. In the current study, the percentage of the total cases that were correctly classified is reported. The evaluation is achieved by calculating both the true and false positives classifications, as shown in the figure below.

Table 6: Classification table

	Confusion Matrix	
	Predicted (No)	Predicted (Yes)
Observed (No)	True Negative (TN)	False Positives (FP)
Observed (Yes)	False Negatives (FN)	True Positive (TP)

The formula below is used to calculate the confusion matrix [227]:

104

$$\text{Model Accuracy Rate} = \frac{TP+TN}{TP+FP+TN+FN}$$

$$\text{Misclassification Rate} = \frac{FP+FN}{TP+FP+TN+FN}$$

$$\text{True Positive Rate (Sensitivity)} = \frac{TP}{TP+FN}$$

$$\text{True Negative Rate (Specificity)} = \frac{TN}{FP+TN}$$

Where Model Accuracy Rate is the % of correct predictions, Misclassification Rate is the % of incorrect predictions. Sensitivity measures the probability for a test to show the presence of a disease in a person who has it and specificity measures that how likely the test shows a person does not have the disease when in fact they are disease free. The main goal of the matrix is to determine with model is the most accurate and with the highest performances classification for diabetes type-II. Neutral Networks models are combined in calculating the final result.

3.5.2. ROC Curve:

The Receiver Operating Characteristic (ROC) curve displays each categorical dependent variable. The curve is created by plotting specificity against sensitivity at various cutoff points. In a logistic regression, the sensitivity and specificity can be evaluated at different levels of predicted probabilities by comparing the predicted classification with the observed classification of the dependent variable. The region under the ROC curve provides a measure of the discriminative ability of the model. The main reason behind the use of the curve is to identify the model with highest performances, which is judged on the basis of the most accurate model of classification [221].

CHAPTER IV

IV. RESULTS

4.1 Overview

This chapter includes the results and their interpretations in order to attain the objective of the study. There are total six dependent variables with binary response (yes and no), these are diabetes with Ketoacidosis, diabetes with hyperosmolarity, diabetes with renal manifestations, diabetes with ophthalmic manifestations, diabetes with neurological manifestations, diabetes with peripheral circulatory disorders, and 13 independent variables Gender (male, female), Race (white, Black, Hispanic, Asian or Pacific Islander, Native American and other), family history of diabetes, obesity, smoking, alcohol related disorders, Hyperlipidemia, Hypertension, Hypercholesterolemia, Asthma, Vitamin D deficiency and age. The significance of these 13 risk factors are tested against each of the diabetes complication. Descriptive statistics of all the independent variables are computed by splitting them into yes and no of the given diabetes complication. Multiple Binary Logistic Regression (Stepwise) is used to calculate the odds ratio and significance of the independent variables. Neural Network results are also given to compare that which model performs well.

4.2 Diabetes Type II with Complication Ketoacidosis:

4.2.1 Descriptive Statistics

Data was collected from a total of 452,223 patients with diabetes type 2 with complications. Of these, 2.9% (12,936) of the total patients were found to have ketoacidosis

(see table 7). The results are further broken down into gender and risk factors that are Obesity, smoking, hypertension, hypercholesterolemia, vitamin D deficiency, asthma, alcohol use, Hyperlipidemia and family history of diabetes.

Table 7: Descriptive analysis for DT2 with ketoacidosis

	Ketoacidosis	%	No Ketoacidosis	%	Total	%
Number of patient	12,936	2.9%	439,287	97.1%	452,223	100.0%
Age (Mean [SD])	58.3[14.5]		67.60[12.65]		67.3[12.7]	
Risk Factors	N	%	N	%	N	%
Family history of diabetes	287	2.2%	3,814	0.9%	4,101	0.9%
Obesity	1,970	15.2%	97,593	22.2%	99,563	22.0%
Smoking	2,064	16.0%	28,898	6.6%	30,962	6.8%
Alcohol	1,478	11.4%	10,741	2.4%	12,219	2.7%
Hypertension	4,910	38.0%	124,478	28.3%	129,388	28.6%
Hypercholesterolemia	728	5.6%	32,548	7.4%	33,276	7.4%
Hyperglyceridemia	319	2.5%	2,609	0.6%	2,928	0.6%
Vitamin d deficiency	101	0.8%	6,162	1.4%	6,263	1.4%
Asthma	810	6.3%	33,974	7.7%	34,784	7.7%
Hyperlipidemia	3,615	27.9%	172,271	39.2%	175,886	38.89%

Of these factors the highest numbers of cases of diabetes mellitus types 2 are from the patients who have hypertension (38%) and Hyperlipidemia (27.9%) too. Similarly, next highest numbers of cases of diabetes mellitus types 2 are from the patients who have smoking (16%), obesity (15.2%) and Alcohol related disorders (11.4%). Risk factors that have least number of cases of diabetes mellitus types 2 are from the patients who have Vitamin d deficiency (0.8%) and Hyperglyceridemia (2.5%).

Young adults (18-24) who made up 0.7% of the total patients were least affected by diabetes type 2 with complication having 0.7% of this age group as affected by ketoacidosis (see Figure 3). The elderly that were above 65 years of age made up 59.8% of the data and this group had 40.3% of the patients diagnosed with ketoacidosis. The group that had the highest number of patients diagnosed with ketoacidosis was the group 50-64 years of age with 40.3 percent of this age group having ketoacidosis. Thus the number of patients that had a high incidence of diabetes mellitus type 2 was above the age of 50 and this constituted 75.2% of the total number of patients that had diabetes mellitus type 2 with ketoacidosis.
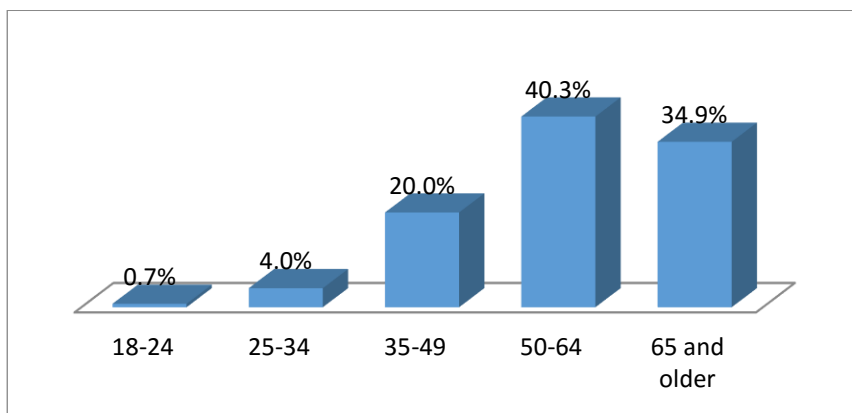
Figure 4: The age distribution of DMT2 with ketoacidosis patients

Whites who were the majority race had the highest figures of those with ketoacidosis at 53.7%. Native Americans, Hispanics and the missing ethnicity had low numbers with ketoacidosis. Black race constituted 16.3% of the total patients and 21.1% of these had diabetes mellitus type 2 with ketoacidosis. Missing ethnicity also had a high incidence of diabetes mellitus type 2 with ketosis which was at 10%. Native Americans had the least number of diabetes mellitus type 2 with complication patients at 0.8% of the total patients from the data and of these an even smaller number had ketoacidosis at 1%.
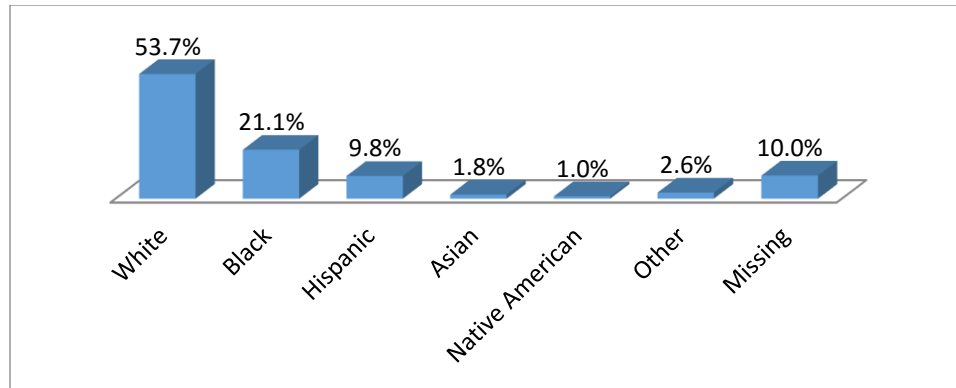
Figure 5: The race distribution of DMT2 with ketoacidosis patients

Males and females were almost equally affected with ketoacidosis. Females represented 52% of the total patients and those affected by ketoacidosis and Males represented 48% of the total patients with diabetes type 2 with Ketoacidosis. The difference between the female and male patients with ketoacidosis was 3% the male's figures being slightly lower.
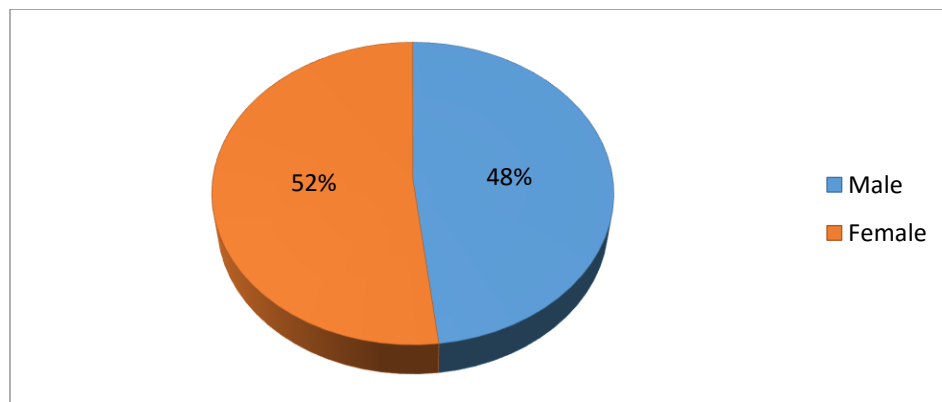
Figure 6: The gender distribution of DMT2 with ketoacidosis patients

4.2.2 Prevalence Rate of Ketoacidosis Complication by Race

Prevalence rate was calculated in order to get a clear picture of occurrence of this diabetic complication in population by race. Figure 7 contains the prevalence rate for each race considered in this study. From the figure it was vibrant that Black ethnic group led with prevalence rate close to the 8 per 100,000 persons followed by the ethnic group Native

America with prevalence rate close to 5.5 per 100,000 person. Hispanic ethnic group had prevalence rate of 3.5 per 100,000 person, white ethnic group had prevalence rate of 3 per 100,000 person and Asian have the lowest prevalence rate of all close to 2 per 100,000. It indicated that a person belong to Black ethnic group was more likely to have Diabetes Type II with Ketoacidosis and Asian were the least likely to have that disease.
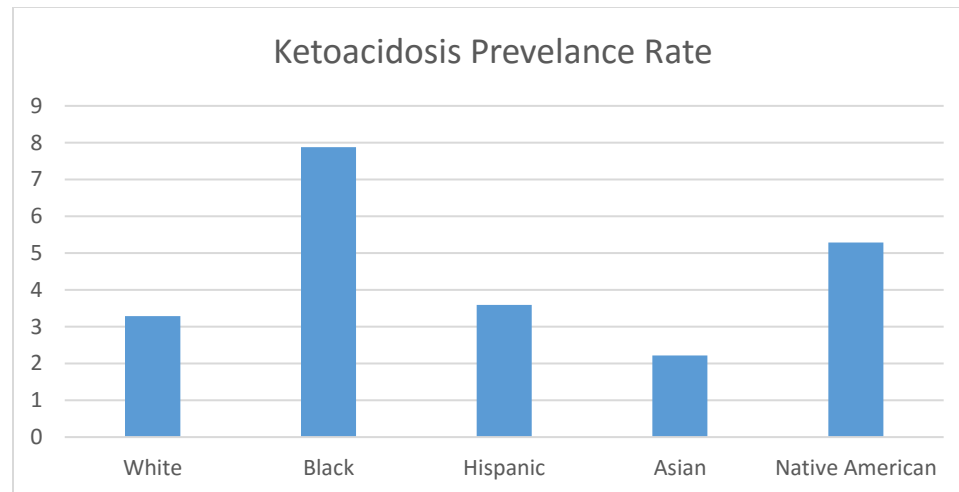
Figure 7: Prevalence rate by race for ketoacidosis

4.2.3 Analysis of Risk Factors for Diabetes Type II with Ketoacidosis

In determine the risk factors for the Diabetes Type II with Ketoacidosis, binary logistic regression (Stepwise) analysis is used. The considered risk factors are Gender (male, female), Race (white, Black, Hispanic, Asian or Pacific Islander, Native American and other), family history of diabetes, obesity, smoking, alcohol related disorders, Hyperlipidemia, Hypertension, Hypercholesterolemia, Asthma, Vitamin D deficiency and age. Logistic regression model assisted to identify that which independent variable is significant in predicting the dependent variable that is Diabetes Type II with Ketoacidosis.

4.2.3.1 Dependent Variable: Diabetes with Type II with Complication Ketoacidosis

In sample data total 12,936 patients' diagnoses as the Diabetes Type II with Ketoacidosis. The dependent variable is binary, so value "1" is assigned to the patients who were diagnosed with the Diabetes Type II with Ketoacidosis and "0" value is assigned to the patients who were not diagnosed with this complication. Both of the genders are considered for this with age 18 and above. The table 8 given below contains all the important information about the significance of the independent variables.

4.2.3.2 Significance of Independent Variables in the Model

All variables and their respective categories listed in table 8 are significantly related to Diabetes Type II with Ketoacidosis, $p < 0.001$, except the two categories of ethnicity that are Asian or Pacific Islander and Native American ($p > 0.05$). The variables under study had different odds ratios with some having higher odd ratios than others. The variables with higher odd ratios had higher chances of developing Diabetes Type II with Ketoacidosis.

Variables including two ethnic groups (black and other), family history of diabetes, smoking, alcohol related disorders, gender, hypertension and hyperglyceridemia, indicated higher odds ratios and hence increased the chances of acquiring Diabetes Type II with Ketoacidosis, p-value < 0.001. Alcohol related disorders had the highest odd ratio 3.303 (C.I: 3.092, 3.528) indicated that patients with Alcohol related disorders had significantly higher risk of developing Diabetes Type II with Ketoacidosis, as compering to the patient who did not had any Alcohol related disorders.

Followed by Hyperglyceridemia with odds ratio 2.992 (C.I: 2.620, 3.416) the family history of diabetes with odds ratio 1.661 (C.I: 1.455, 1.895), family history of

diabetes with odds ratio 1.661 (C.I: 1.455, 1.895), hypertension with odds ratio 1.549 (C.I: 1.488 1.613), gender with odds ratio 1.233 (C.I: 1.187, 1.282) and smoking with odds ratio 1.149 (C.I: 1.087, 1.214). All the variables described above are significantly related with diabetes type II with Ketoacidosis, p-value < 0.001.

Table 8: Odds ratio estimates for DMT2 with ketoacidosis

	Odds Ratio	p-value	95% C.I. for OR Lower	Upper
Gender [Female]	1.233	.000	1.187	1.282
White		.000		
Black	1.111	.000	1.060	1.165
Hispanic	.934	.033	.877	.994
Asian or Pacific Islander	.977	.736	.853	1.119
Native American	.934	.464	.779	1.121
Other	1.236	.000	1.103	1.384
Family history of diabetes mellitus	1.661	.000	1.455	1.895
Obesity	.520	.000	.493	.548
Smoking	1.149	.000	1.087	1.214
Alcohol related disorders	3.303	.000	3.092	3.528
Hyperlipidemia	.621	.000	.595	.648
Hypertension	1.549	.000	1.488	1.613
Hypercholesterolemia	.679	.000	.626	.736
Hyperglyceridemia	2.992	.000	2.620	3.416
Asthma	.656	.000	.606	.710
Vitamin D deficiency	.580	.000	.469	.717
18-24		.000		
25-34	.320	.000	.241	.425
35-49	.152	.000	.116	.199
50-64	.082	.000	.063	.107
65 and older	.039	.000	.030	.050

Out of all the participating ethnic groups only two appeared to be the significantly related when compared to the white race (p-value < 0.001). Black race with odds ratio 1.111 (C.I: 1.060, 1.165) and others ethnic group with odds ratio 1.236 (C.I: 1.103, 1.384).

Ethnic groups Hispanic, Asian or Pacific Islander and Native American was insignificantly related with the diabetes type II with Ketoacidosis, (p-value > 0.05).

Variables age, vitamin d deficiency, asthma, hypercholesterolemia, hyperlipidemia and obesity are the one with low odd ratios. Age had the lowest odd ratio as indicated by the various age group participants, p-value < 0.01. According to Table 8, all participating age groups had decreased chances of developing Diabetes Type II. The odd ratios were different per group. The 25-34 age group had an odds ratio 0.320 (C.I: 0.241, 0.425) followed by 35-49 age group with odds ratio 0.152 (C.I: 0.116, 0.199), 50-64 age group with an odd ratio of 0.082 (C.I: 0.063, 0.107) and 65 and older age group with odds ratio 0.039 (C.I: 0.030, .050). The mentioned age groups were being compared to the 18-24 age group. All the age group categories are also significantly associated, p-value < 0.001
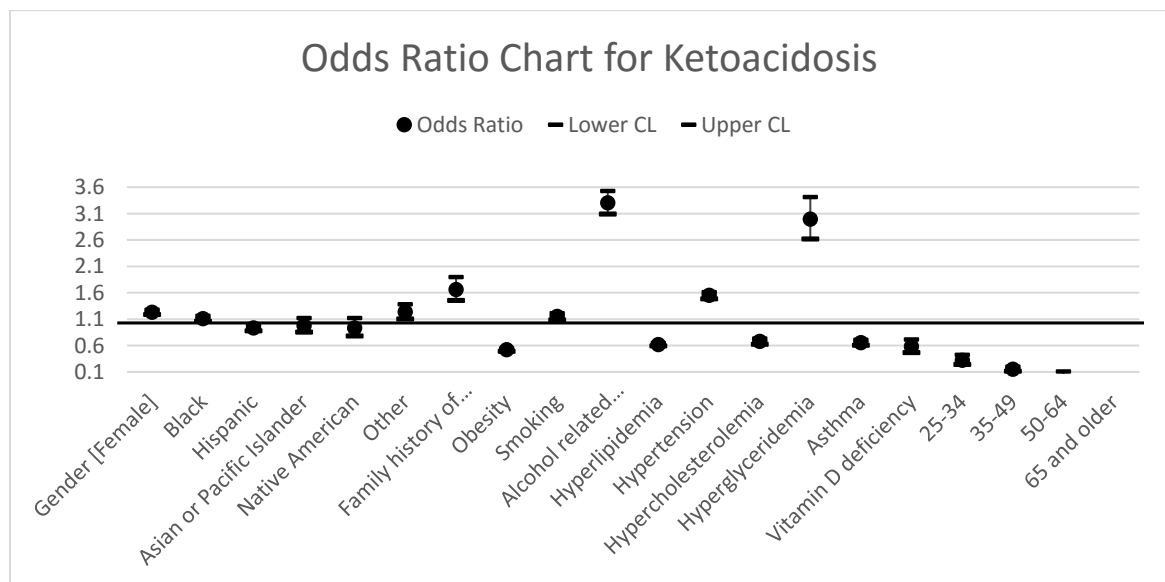
Figure 8: Odds ratios result chart for DMT2 with ketoacidosis

Obese patients had lower risks of being associated with the complication when compared to those who were not obese. This variable had an odd ratio of 0.520 (C.I: 0.493, 0.548).

Hyperlipidemia and Hypercholesterolemia patients were also at a low risk of developing

diabetes type II with Ketoacidosis with odds ratio 0.621 and 0.679 respectively. The risk

of developing Diabetes Type II with Ketoacidosis for patients with Asthma decreased by

0.656 when compared to patients who were not ailing from Asthma and for patients with

Vitamin D deficiency decreased by 0.580 when compared to patients who were not ill from

Vitamin D deficiency. For variables with lower odd ratios all had a ratio of ($p < 0.001$).

4.3 Diabetes Type II with Complication Hyperosmolarity:

4.3.1 Descriptive Statistics

Data was collected from a total of 452,223 patients with diabetes type 2 with complications.

Of these, 1.4% (6,478) of the total patients were found to have Hyperosmolarity (see table

9).

Table 9: Descriptive analysis for DMT2 with hyperosmolarity

	Hyperosmolarity	%	No Hyperosmolarity	%	Total	
Number of patient	6478	1.4%	445745	98.6%	452223	100%
Mean [SD] age	65.6[14.7]		67.39[12.74]		67.3[12.7]	
Risk Factors	N	%	N	%	N	%
Family History of diabetes	120	1.9%	3981	0.9%	4101	0.9%
Obesity	1047	16.2%	98516	22.1%	99563	22.0%
Smoking	794	12.3%	30168	6.8%	30962	6.8%
Alcohol	432	6.7%	11787	2.6%	12219	2.7%
Hypertension	2283	35.2%	127105	28.5%	129388	28.6%
Hypercholesterolemia	371	5.7%	32905	7.4%	33276	7.4%
Hyperglyceridemia	93	1.4%	2835	0.6%	2928	0.6%
Vitamin d deficiency	49	0.8%	6214	1.4%	6263	1.4%
Asthma	428	6.6%	34356	7.7%	34784	7.7%
Hyperlipidemia	1940	29.9%	173946	39%	175886	38.8%

From all of the risk factors the highest numbers of cases of diabetes mellitus types 2 are

from the patients who have hypertension (35.2%) and Hyperlipidemia (29.9%). Similarly,

next highest numbers of cases of diabetes mellitus types 2 are from the patients who are

obese (16.2%) and smoker (12.3%). Risk factors that have least number of cases of diabetes mellitus types 2 are from the patients who have Vitamin d deficiency (0.8%) and Family History of diabetes (1.9%).
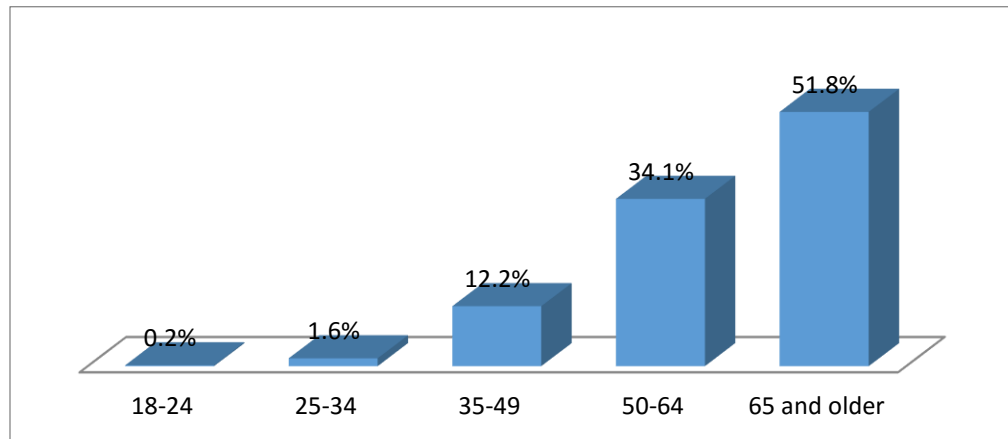
Figure 9: The age distribution of DMT2 with hyperosmolarity patients

Young adults (18-24) who made up 0.1% of the total patients were least affected by diabetes type 2 with complication having 0.2% of this age group as affected by Hyperosmolarity. The group 50-64 years made up 31.2% of the data and this group had 34.1% of the patients diagnosed with Hyperosmolarity. The group that had the highest number of patients diagnosed with Hyperosmolarity was the group 65 years and older of age with 51.8 percent of this age group having Hyperosmolarity.
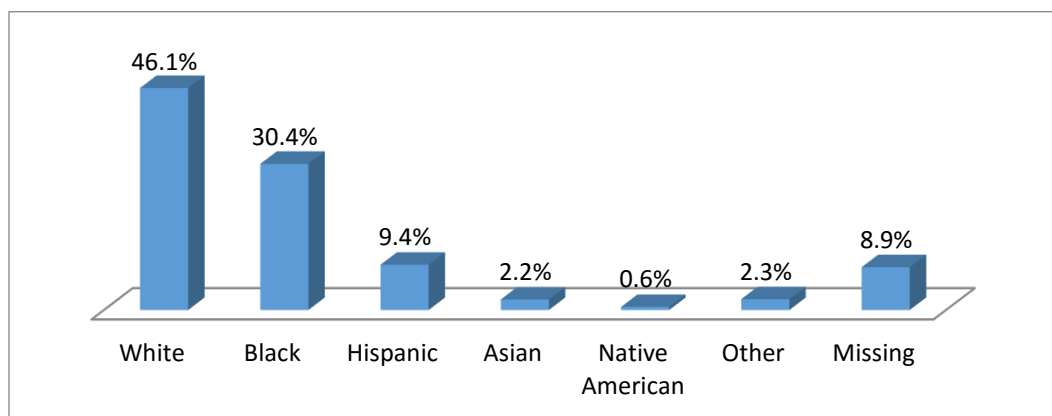
Figure 10: The race distribution of DMT2 with hyperosmolarity patients

Whites who were the majority race had the highest figures of those with Hyperosmolarity at 46.1%. Native Americans, Hispanics, Asian and the missing ethnicity had low numbers with Hyperosmolarity. Black race constituted 16.3% of the total patients and 30.4% of these had diabetes mellitus type 2 with Hyperosmolarity. Hispanics ethnicity also had a high incidence of diabetes mellitus type 2 with Hyperosmolarity which was at 9.4%. Native Americans had the least number of diabetes mellitus type 2 with complication patients at 0.8% of the total patients from the data and of these an even smaller number had Hyperosmolarity at 0.6%.
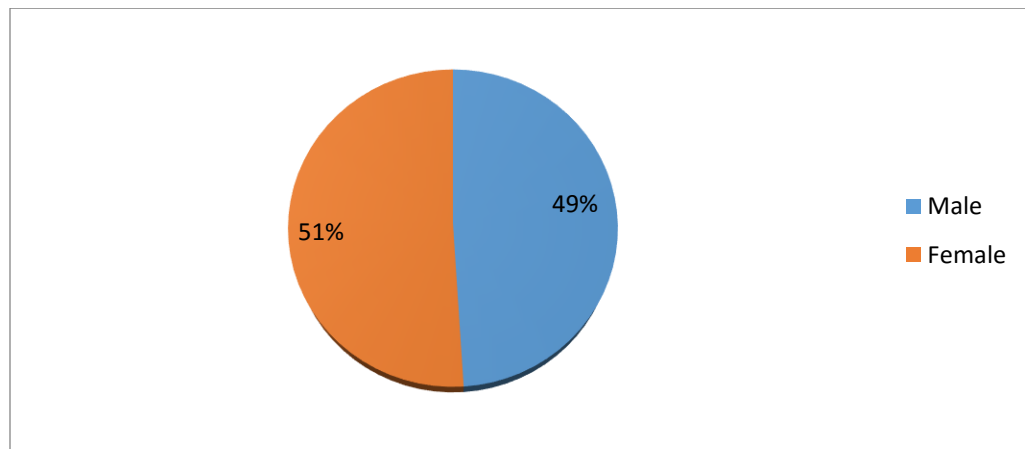
Figure 11: The gender distribution of DMT2 with hyperosmolarity patients

Males and females were almost equally affected with Hyperosmolarity. Females represented 51% of the total patients and those affected by Hyperosmolarity and Males represented 49% of the total patients with diabetes type 2 with Hyperosmolarity. The difference between the female and male patients with Hyperosmolarity was 2% the male's figures being slightly lower.

4.3.2 Prevalence of Hyperosmolarity Complication by Race

Figure 12 contains the prevalence rate for each race considered in this study. From the figure it was vibrant that Black ethnic group led with prevalence rate close to the 5.5 per

100,000 persons followed by the ethnic group Hispanic with prevalence rate close to 1.7 per 100,000 person. Native America ethnic group had prevalence rate of 1.6 per 100,000 person, white ethnic group had prevalence rate of 1.4 per 100,000 person and Asian have the lowest prevalence rate of all close to 1.3 per 100,000. It indicated that a person belong to Black ethnic group was more likely to have Diabetes Type II with Hyperosmolarity and Asian were the least likely to have that disease.
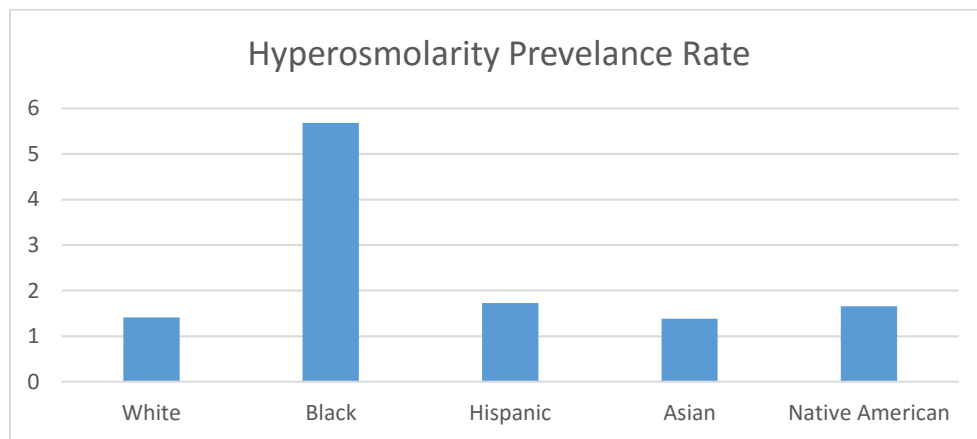
Figure 12: Prevalence rate by race for hyperosmolarity

4.3.3 Analysis of Risk Factors for Diabetes Type II with Hyperosmolarity

In determine the risk factors for the Diabetes Type II with Hyperosmolarity, binary logistic regression analysis is used. The same risk factors are considered that were considered before. Logistic regression model assisted to identify that which independent variable is significant in predicting the dependent variable that is Diabetes Type II with Hyperosmolarity.

4.3.3.1 Dependent Variable: Diabetes Type II with Complication Hyperosmolarity

In sample data total 12936 patients' diagnoses as the Diabetes Type II with Hyperosmolarity. The dependent variable is treated in the same way as the pervious one like binary. Both of the genders are considered for this with age 18 and above. The table

10 given below contains all the important information about the significance of the independent variables.

4.3.3.2 Significance of Independent Variables in the Model

All variables and their respective categories listed in table 10 are significantly related with Diabetes Type II with Hyperosmolarity, $p < 0.001$, except one categories of ethnicity that was Native American and three categories of age that were 25-34 and 35-49 years old ($p > 0.05$). The variables under study had different odds ratios with some having higher odd ratios than others. The variables with higher odd ratios had higher chances of developing Diabetes Type II with Hyperosmolarity.

Variables including ethnic groups (excluding the category of Native American), family history of diabetes, smoking, alcohol related disorders, gender, hypertension and hyperglyceridemia, indicated higher odds ratios and hence increased the chances of acquiring Diabetes Type II with Hyperosmolarity. Hyperglyceridemia had the highest odds ratio 2.193 (C.I: 1.754, 2.741) followed by Alcohol related disorders with odds ratio 2.006 (C.I: 1.796, 2.239) indicated that patients with Alcohol related disorders had significantly higher risk of developing Diabetes Type II with Hyperosmolarity, as compering to the patient who did not had any Alcohol related disorders.

The family history of diabetes with odds ratio 1.592 (C.I: 1.313, 1.932), hypertension with odds ratio 1.539 (C.I: 1.456 1.627), smoking with odds ratio 1.124 (C.I: 1.033, 1.222) and gender with odds ratio 1.062 (C.I: 1.007, 1.119). All the variables described above are significantly related with diabetes type II with Hyperosmolarity with p-value < 0.001 except the smoking with p-value < 0.05.

Table 10: Odds ratio estimates for DMT2 with hyperosmolarity

	Odds Ratio	Sig.	95.0% C.I.for Odds Ratio	
			Lower	Upper
Gender [Female]	1.062	0.027	1.007	1.119
White		.000		
Black	2.301	.000	2.169	2.442
Hispanic	1.225	.000	1.121	1.338
Asian or Pacific Islander	1.348	.001	1.137	1.598
Native American	.929	.641	.680	1.268
Other	1.358	.000	1.148	1.606
Family history of diabetes mellitus	1.592	.000	1.313	1.932
Obesity	.655	.000	.610	.704
Smoking	1.124	.006	1.033	1.222
Alcohol related disorders	2.006	.000	1.796	2.239
Hyperlipidemia	.672	.000	.635	.712
Hypertension	1.539	.000	1.456	1.627
Hypercholesterolemia	.671	.000	.600	.751
Hyperglyceridemia	2.193	.000	1.754	2.741
Asthma	.778	.000	.700	.864
Vitamin D deficiency	.501	.000	.366	.684
18-24		.000		
25-34	.667	.217	.350	1.268
35-49	.597	.098	.323	1.101
50-64	.481	.019	.262	.886
65 and older	.423	.006	.230	.779

Out of all the participating ethnic groups only one category Native American was insignificant p-value > 0.05 while the rest of the ethnic groups were significantly associated with an increased chance of developing diabetes type II with Hyperosmolarity as compare to white. Black race with odds ratio 2.301 (C.I: 2.169, 2.442), Asian or Pacific Islander with odds ratio 1.225 (C.I: 1.121, 1.338) and others ethnic group with odds ratio 1.358 (C.I: 1.148, 1.606). Ethnic group Native American was insignificantly related with the diabetes type II with Hyperosmolarity, (p-value > 0.05).

Variables age (with two insignificant categories), vitamin d deficiency, asthma, hypercholesterolemia, hyperlipidemia and obesity were the one with low odd ratios. Age had the lowest odd ratio as indicated by two age group participants that were significant, p-value < 0.05. According to Table 9, all participating age groups had decreased chances of developing Diabetes Type II. The odd ratios were different per group. The 50-64 age group with an odd ratio of 0.481 (C.I: 0.262, 0.886) and 65 and older age group with odds ratio 0.423 (C.I: 0.230, .779). The mentioned age groups were being compared to the 18-24 age group. Only two age group categories are also significantly associated, p-value < 0.05.
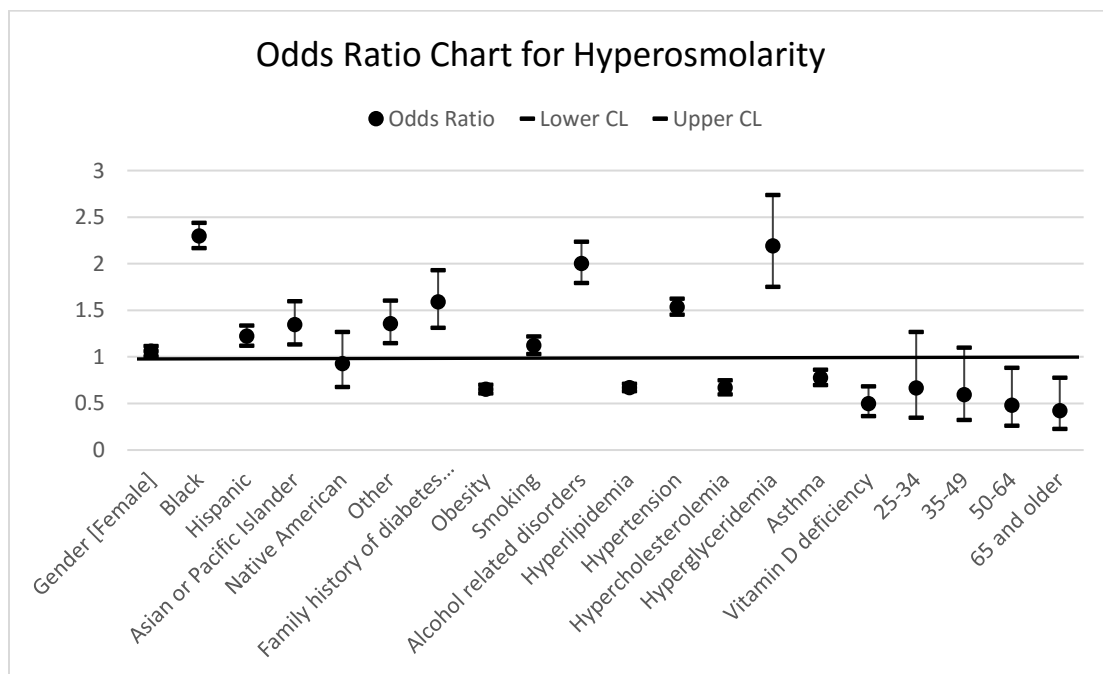
Figure 13: Odds ratio results chart for hyperosmolarity

Obese patients had lower risks of being associated with the complication when compared to those who were not obese. This variable had an odd ratio of 0.655 (C.I: 0.610, 0.704). Hyperlipidemia and Hypercholesterolemia patients were also at a low risk of developing diabetes type II with Hyperosmolarity with odds ratio 0.672 and 0.671

respectively. The risk of developing Diabetes Type II with Ketoacidosis for patients with

Asthma decreased by 0.778 when compared to patients who were not ailing from Asthma

and for patients with Vitamin D deficiency decreased by 0.501 when compared to patients

who were not ill from Vitamin D deficiency. For variables with lower odd ratios all had a

ratio of $(p < 0.001)$ except age with p-value < 0.05.

4.4 Diabetes Type II with Complication Renal Manifestations:

4.4.1 Descriptive Statistics

Data was collected from a total of 452,223 patients with diabetes type 2 with complications.

Of these, 32.8% (148,283) of the total patients were found to have Renal Manifestations

(see table 11).

Table 11: Descriptive statistics for DMT2 with renal manifestations

	Renal	%	No Renal	%	Total	%
Number of patient	148283	32.8%	303940	67.2%	452223	100.0%
Mean [SD] age	68.9[12.1]		66.6[12.9]		67.3[12.7]	
	N	%	N	%	N	%
Risk Factors						
Family History of diabetes	1108	0.7%	2993	1.0%	4101	0.9%
Obesity	29452	19.9%	70111	23.1%	99563	22.0%
Smoking	9249	6.2%	21713	7.1%	30962	6.8%
Alcohol	2553	1.7%	9666	3.2%	12219	2.7%
Hypertension	8511	5.7%	120877	39.8%	129388	28.6%
Hypercholesterolemia	9838	6.6%	23438	7.7%	33276	7.4%
Hyperglyceridemia	672	0.5%	2256	0.7%	2928	0.6%
Vitamin d deficiency	2428	1.6%	3835	1.3%	6263	1.4%
Asthma	9840	6.6%	24944	8.2%	34784	7.7%
Dyslipidemia	56732	38.3%	119154	39.2%	175886	38.8%

From all of the risk factors the highest numbers of cases of diabetes mellitus types 2 are

from the patients who have Hyperlipidemia (38.3%) and Obesity (19.9%).

Hypercholesterolemia and Asthma have same percentage of patients (6.6%) who have

diabetes mellitus types 2. Risk factors that have least number of cases of diabetes mellitus types 2 are from the patients who have Hyperglyceridemia (0.5%), Family History of diabetes (0.7%) and Vitamin d deficiency (1.6%). Young adults (18-24) who made up 0.1% of the total patients were least affected by diabetes type 2 with complication having 0.0% of this age group as affected by renal. The group 50-64 years made up 82.1% of the data and this group had 28.1% of the patients diagnosed with renal.

The group that had the highest number of patients diagnosed with renal was the group 65 years and older of age with 65.3 percent of this age group having renal. Thus the number of patients that had a high incidence of diabetes mellitus type 2 with renal was above the age of 65 and this constituted 65.3% of the total number of patients that had diabetes mellitus type 2 with renal.
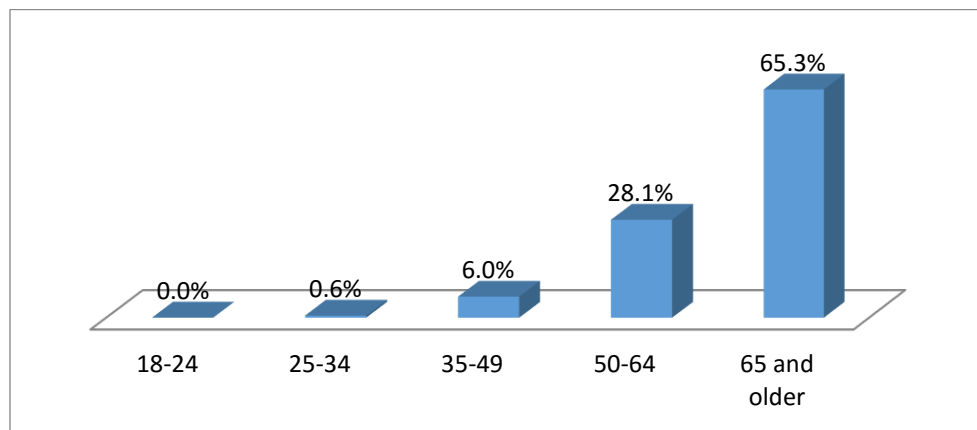
Figure 14: The age distribution of DMT2 with renal manifestations patients

Whites who were the majority race had the highest figures of those with renal at 51.9%. Native Americans, Hispanics, Asian and the missing ethnicity had low numbers with renal. Black race constituted 16.3% of the total patients and 18.6% of these had diabetes mellitus type 2 with renal.
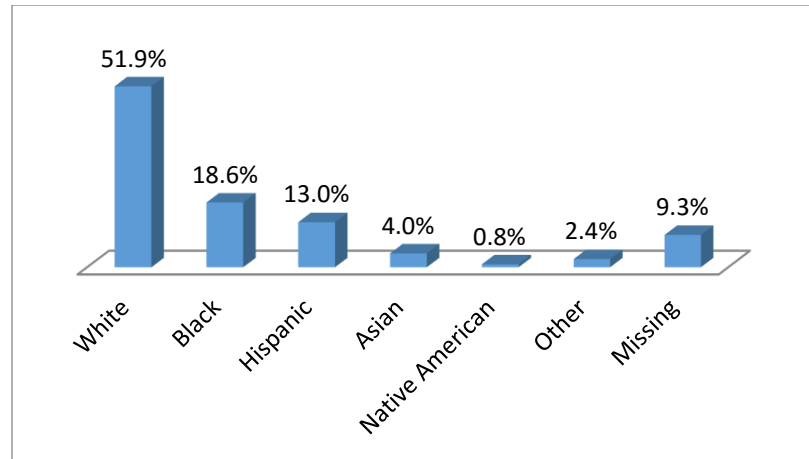
Figure 15: The race distribution of DMT2 with renal manifestations patients

Hispanics ethnicity also had a high incidence of diabetes mellitus type 2 with renal which was at 13.0%. Native Americans had the least number of diabetes mellitus type 2 with complication patients at 0.8% of the total patients from the data and of these an even smaller number had renal at 2.4%.
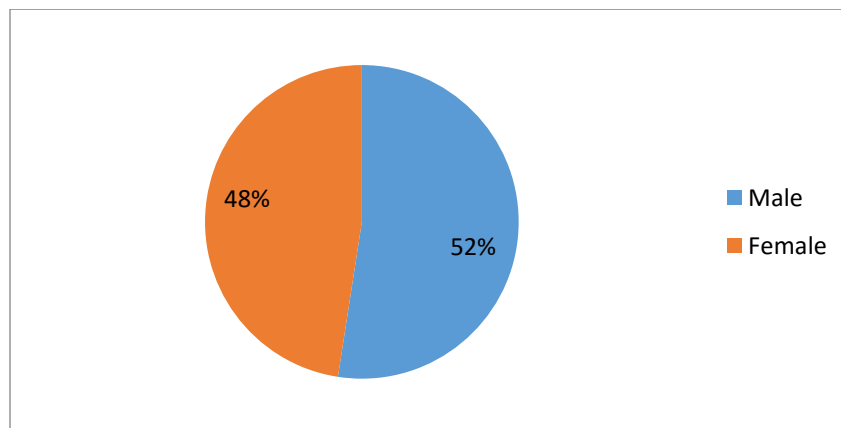
Figure 16: The gender distribution of DMT2 with renal manifestations patients

Males and females were almost equally affected with renal. Males represented 52% of the total patients and those affected by renal and Females represented 48% of the total patients with diabetes type 2 with renal. The difference between the female and male patients with renal was 4% the female's figures being slightly lower.

4.4.2 Prevalence Rate of Renal Manifestations Complication by Race

Figure 17 contains the prevalence rate for each race considered in this study. From the figure it was clear that Black ethnic group led with prevalence rate close to the 80 per 100,000 persons followed by the ethnic group Asian with prevalence rate close to 57 per 100,000 person. Hispanic ethnic group had prevalence rate of 54 per 100,000 person, Native American ethnic group had prevalence rate of 50 per 100,000 person and White have the lowest prevalence rate of all close to 36 per 100,000. It indicated that a person belong to Black ethnic group was more likely to have Diabetes Type II with Renal Manifestations and White people were the least likely to have that disease.
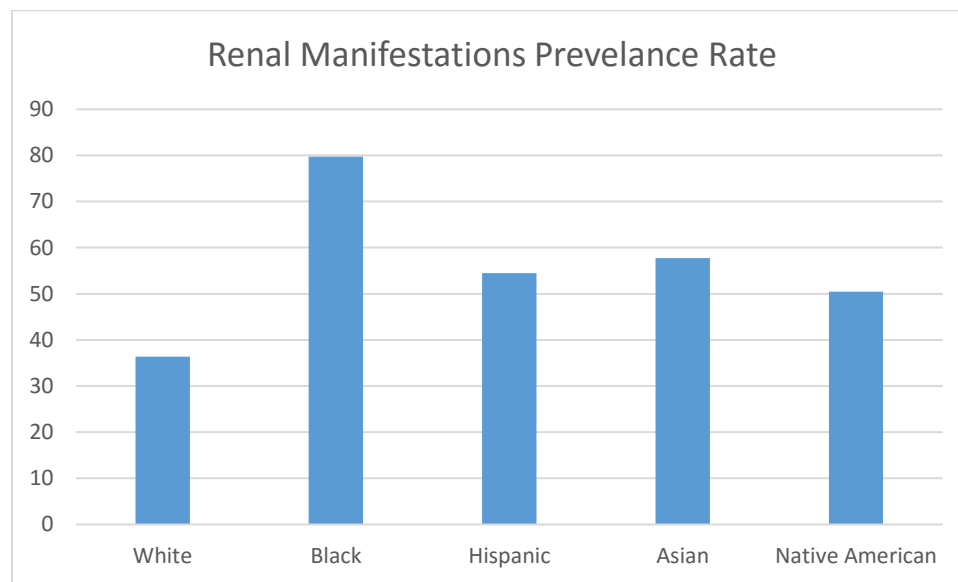
Figure 17: Prevalence rate by race for renal manifestations

4.4.3 Analysis of Risk Factors for Diabetes Type II with Renal Manifestations

In determine the risk factors for the Diabetes Type II with Renal Manifestations, binary logistic regression analysis is used. The same risk factors are considered that were considered before. Logistic regression model assisted to identify that which independent

variable is significant in predicting the dependent variable that is Diabetes Type II with Renal Manifestations.

4.4.3.1. Dependent variable: Diabetes Type II with Renal Manifestations

In sample data total 148283 patients' diagnoses as the Diabetes Type II with Renal Manifestations out of 452232. The dependent variable is binary, so value "1" is assigned to the patients who were diagnosed with the Diabetes Type II with Renal Manifestations and "0" value is assigned to the patients who were not diagnosed with this complication. Both of the genders are considered for this with age 18 and above. The table 12 given below contains all the important information about the significance of the independent variables.

4.4.3.2 Significance of Independent Variables in the Model

All variables indicated in Table 2 were importantly related to Diabetes Type II with Renal Manifestations ($p < 0.05$). However, family histories associated with both asthma and diabetes were excluded from the model ($p > 0.05$) since they were insignificant. The variables under investigation had different odds ratios with some indicating higher odd ratios than others. The variables with higher odd ratios had higher chances of developing Diabetes Type II with Renal Manifestations.

Variables including ethnic groups, obesity, hyperlipidemia, hypercholesterolemia, Vitamin D deficiency and age indicated higher odds ratios and hence increased chances of acquiring Diabetes Type II with Renal Manifestations. Age had the highest odd ratio as indicated by the various age group participants. According to Table 12, all participating age groups had increased chances of developing Diabetes Type II. The odd ratios were different per group. The 65 and other age group had a ratio of 3.586, followed by 50-64 age group with an odd ratio of 2.724. The 35-49 age group followed closely with an odd

ratio of 2.101 and lastly the 25-34 age group with an odd ratio of 1.951. The mentioned age groups were being compared to the 18-24 age group.

Table 12: Odds ratio estimates for DMT2 with renal manifestations

| | Odds ratio | p-value | 95.0% C.I. for Odds ratio | |
			Lower	Upper
Gender [Female]	.886	.000	.874	.899
White		.000		
Black	1.439	.000	1.413	1.466
Hispanic	1.924	.000	1.881	1.968
Asian or Pacific Islander	3.159	.000	3.022	3.303
Native American	1.550	.000	1.436	1.672
Other	1.393	.000	1.331	1.459
Obesity	1.049	.000	1.031	1.068
Smoking	.850	.000	.826	.875
Alcohol related disorders	.693	.000	.659	.729
Hyperlipidemia	1.177	.000	1.160	1.195
Hypertension	.096	.000	.094	.098
Hypercholesterolemia	1.057	.000	1.027	1.087
Hyperglyceridemia	.899	.037	.813	.994
Vitamin D deficiency	1.372	.000	1.293	1.457
18-24		.000		
25-34	1.951	.000	1.368	2.782
35-49	2.101	.000	1.487	2.968
50-64	2.724	.000	1.930	3.846
65 and older	3.586	.000	2.540	5.061

Hyperlipidemia had the second highest odd ratio of 1.177 (C.I: 1.160, 1.195) followed by vitamin D deficiency variable with an odd ratio of 1.372 (C.I: 1.293, 1.457). Hypercholesterolemia followed with an odd ratio of 1.057 (C.I: 1.027, 1.087). The obesity variable was also importantly related to Diabetes Type II with an odd ratio of 1.049 (C.I: 1.031, 1.068). All participating ethnic groups had heightened levels of developing Diabetes Type II with renal manifestations when compared to the white race. The Asians or Pacific

Islander led with an odd ratio of 3.159 followed by Hispanic with 1.924. The Native

Americans had an odd ratio of 1.550, Blacks 1.439 and other races 1.393. All variables that

were importantly associated with Diabetes had a ratio of ($p < 0.001$) except for vitamin D

deficiency which had a ratio of $p < 0.000$).

Variables with low odd ratios compared two sets of groups. The gender variable

compared males and females. It had an odd ratio of 0.886 (CI: 0.874, 0.899) indicating that

females had lower chances of being associated with Diabetes Type II with renal

manifestations compared to males. The smoking variable compared the smokers to non-

smokers. It had an odd ratio of 0.850 (C.I: 0.826, 0.875) indicating that smokers were at a

low risk of being associated with the complication compared to non-smokers.
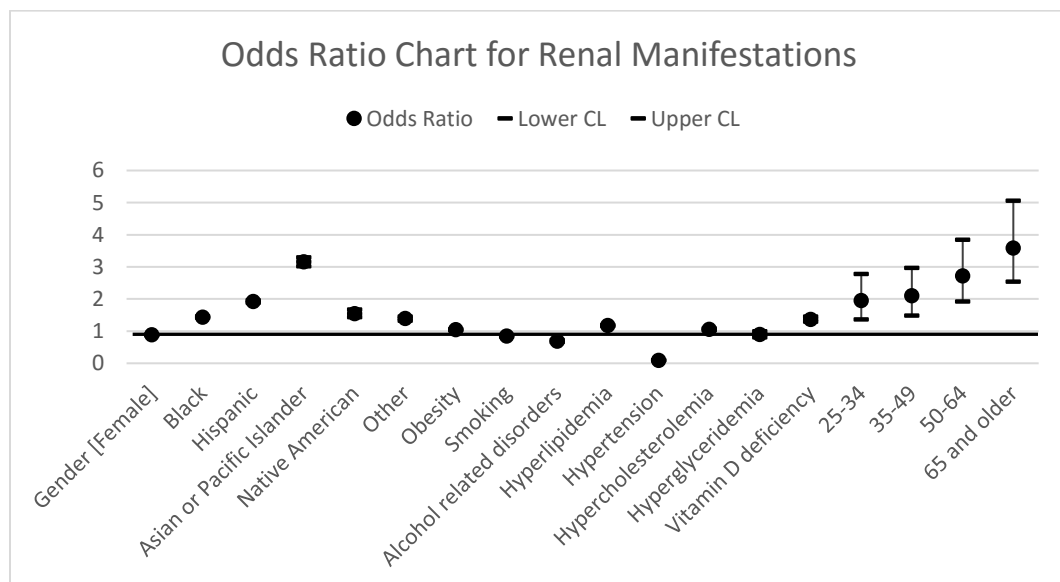
Figure 18: Odds ratio results chart for DMT2 renal manifestations

Patients with alcohol related disorders had lower risks of being associated with the

complication when compared to those who did not have alcohol related disorders. This

variable had an odd ratio of 0.693 (C.I: 0.659, 0.729). Hypertension patients were at a low

risk of developing Diabetes Type II by 0.096 compared to those who did not have

hypertension complications. The odd ratio was 0.096 (C.I: 0.094, 0.098). The risk of developing Diabetes Type II with renal manifestations for patients with hyperglyceridemia decreased by 0.899 when compared to patients who were not ailing from hyperglyceridemia. For variables with lower odd ratios only the gender variable had a ratio of ($p < 0.05$) while others had a ratio of ($p < 0.001$).

4.5 Diabetes Type II with Complication Ophthalmic Manifestations:

4.5.1 Descriptive Statistics

Data was collected from a total of 452,223 patients with diabetes type 2 with complications. Of these, 32.8% (148283) of the total patients were found to have Ophthalmic Manifestations (see table 13). From all of the risk factors the highest numbers of cases of diabetes mellitus types 2 are from the patients who have Hyperlipidemia (43.5%), Hypertension (30.5%) and obesity (21.6%). Risk factors that have least number of cases of diabetes mellitus types 2 are from the patients who have Hyperglyceridemia (0.5%), Vitamin d deficiency (1.5%) and Alcohol related disorders (1.6%).

Table 13: Descriptive statistics for DMT2 with ophthalmic manifestations

	Ophthalmic	%	No Ophthalmic	%	Total	%
Number of patient	28666	6.3%	423557	93.7%	452223	100%
Mean [SD] age	67.2[12.3]		67.37[12.81]		67.3[12.7]	
	N	%	N	%	N	%
Risk Factors						
Family History of diabetes	304	1.1%	3797	0.9%	4101	0.9%
Obesity	6187	21.6%	93376	22.0%	99563	22.0%
Smoking	1719	6.0%	29243	6.9%	30962	6.8%
Alcohol	461	1.6%	11758	2.8%	12219	2.7%
Hypertension	8732	30.5%	120656	28.5%	129388	28.6%
Hypercholesterolemia	2376	8.3%	30900	7.3%	33276	7.4%
Hyperglyceridemia	139	0.5%	2789	0.7%	2928	0.6%
Vitamin d deficiency	442	1.5%	5821	1.4%	6263	1.4%
Asthma	2115	7.4%	32669	7.7%	34784	7.7%
Hyperlipidemia	12478	43.5%	163408	38.6%	175886	38.8%
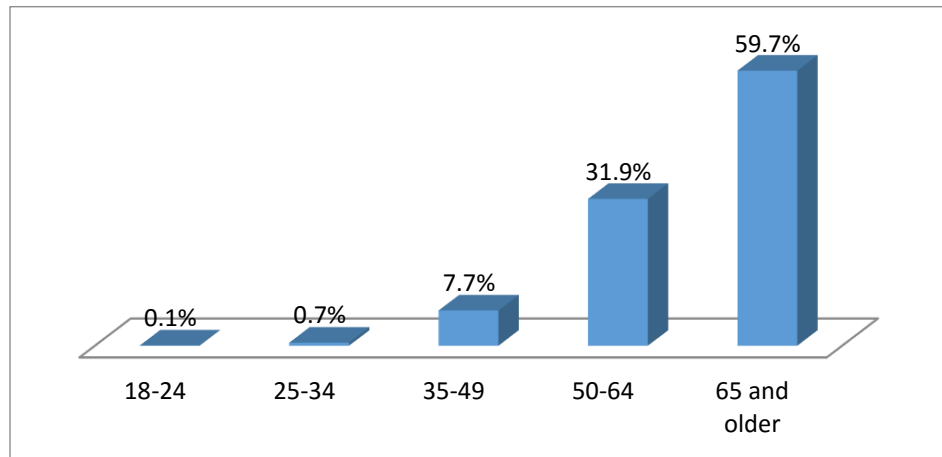
Figure 19: The age distribution of DMT2 with ophthalmic manifestations patients

Young adults (18-24) who made up 0.1% of the total patients were least affected by diabetes type 2 with complication having 0.1% of this age group as affected by ophthalmic. The group 50-64 years made up 31.2% of the data and this group had 31.9% of the patients diagnosed with ophthalmic. The group that had the highest number of patients diagnosed with ophthalmic was the group 65 years and older of age with 51.8 percent of this age group having ophthalmic. Thus the number of patients that had a high incidence of diabetes mellitus type 2 with ophthalmic was above the age of 50 and this constituted 85.9% of the total number of patients that had diabetes mellitus type 2 with ophthalmic.
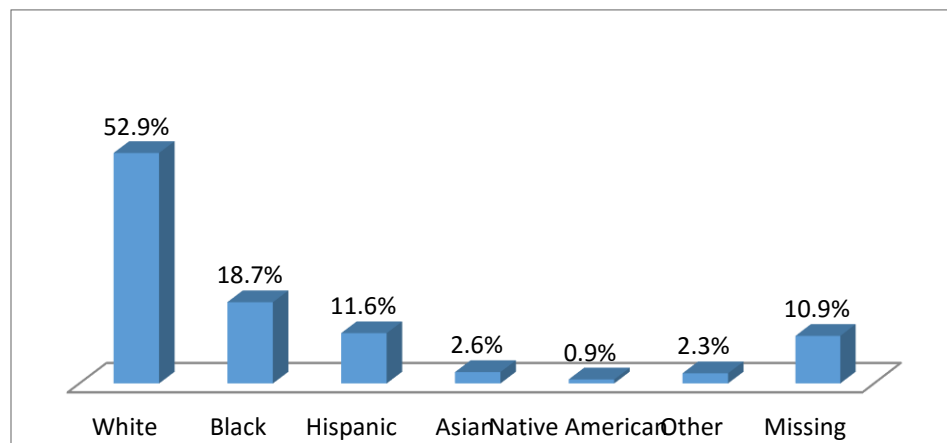
Figure 20: The race distribution of DMT2 with ophthalmic manifestations patients

Whites who were the majority race had the highest figures of those with ophthalmic at 52.9%. Native Americans, Hispanics, Asian and the missing ethnicity had low numbers with ophthalmic. Black race constituted 16.3% of the total patients and 18.7% of these had diabetes mellitus type 2 with ophthalmic Hispanics ethnicity also had a high incidence of diabetes mellitus type 2 with ophthalmic which was at 11.6%. Native Americans had the least number of diabetes mellitus type 2 with complication patients at 0.8% of the total patients from the data and of these an even smaller number had ophthalmic at 0.9%.
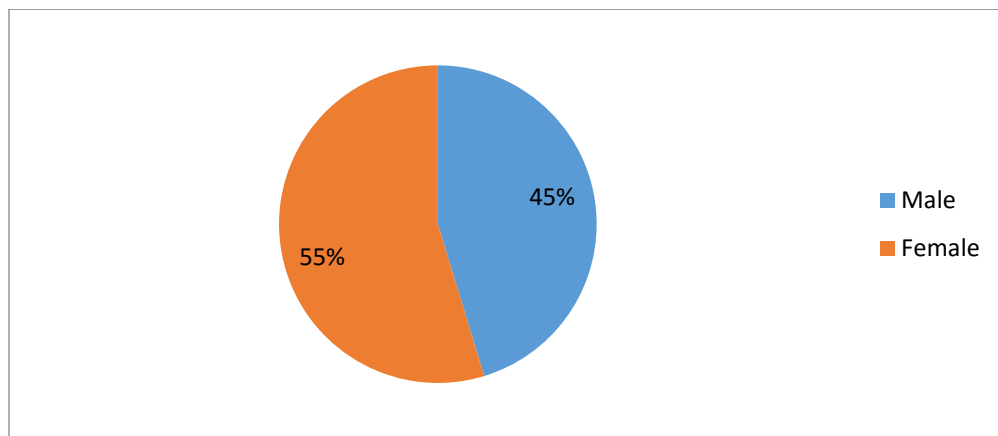
Figure 21: The gender distribution of DMT2 with ophthalmic manifestations patients

Males and females were almost equally affected with ophthalmic. Females represented 55% of the total patients and those affected by ophthalmic and Males represented 45% of the total patients with diabetes type 2 with ophthalmic. The difference between the female and male patients with ophthalmic was 10% the male's figures being lower.

4.5.2 Prevalence Rate of Ophthalmic Manifestations Complication by Race

Figure 22 contains the prevalence rate for each race considered in this study. From the figure it was clear that Black ethnic group led with prevalence rate close to the 15 per 100,000 persons followed by the ethnic group Native American with prevalence rate close to 10 per 100,000 person. Hispanic ethnic group had prevalence rate of 9.3 per 100,000

person, Asian ethnic group had prevalence rate of 7.3 per 100,000 person and White have the lowest prevalence rate of all close to 7.1 per 100,000. It indicated that a person belong to Black ethnic group was more likely to have Diabetes Type II with Ophthalmic Manifestations and White people were the least likely to have that disease.
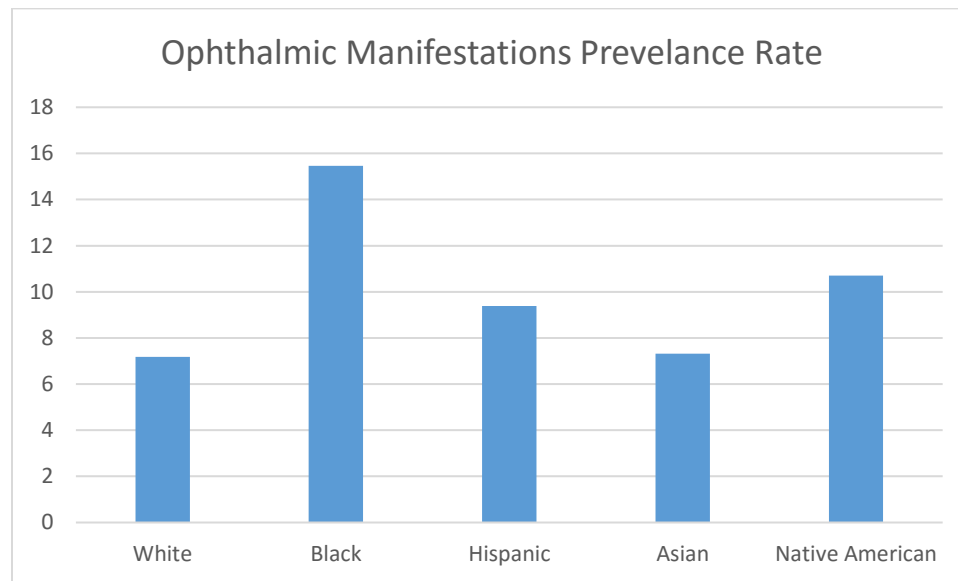
Figure 22: Prevalence rate by race for ophthalmic manifestations

4.5.3 Analysis of Risk Factors for Diabetes Type II with Ophthalmic Manifestations

In determine the risk factors for the Diabetes Type II with Ophthalmic Manifestations, binary logistic regression analysis is used. The same risk factors are considered that were considered before. Logistic regression model assisted to identify that which independent variable is significant in predicting the dependent variable that is Diabetes Type II with Ophthalmic Manifestations.

4.5.3.1. Dependent variable: Diabetes Type II with Ophthalmic Manifestations

In sample data total 148283 patients' diagnoses as the Diabetes Type II with Ophthalmic Manifestations out of 452232. The dependent variable is binary, so value "1" is assigned to the patients who were diagnosed with the Diabetes Type II with Ophthalmic

Manifestations and "0" value is assigned to the patients who were not diagnosed with this complication. Both of the genders are considered for this with age 18 and above. The table14 contains all the important information about the significance of the independent variables.

4.5.3.2 Significance of Independent Variables in the Model

All variables given in table 14 were significantly related with Diabetes Type II with Ophthalmic Manifestations, $p < 0.001$, except age, $p > 0.05$. Variable vitamin D deficiency is not included in the model because it was not strongly associated with Diabetes Type II with Ophthalmic Manifestations. All the variables had different odds ratios with higher odd ratios had higher chances of developing Diabetes Type II with Ophthalmic Manifestations.

Variables including ethnic groups, family history of diabetes, gender, hyperlipidemia, hypertension and Hypercholesterolemia, indicated higher odds ratios and hence increased the chances of getting Diabetes Type II with Ophthalmic Manifestations. Ethnic groups had the highest odds ratio. All participating ethnic groups had heightened levels of developing Diabetes Type II with Ophthalmic Manifestations when compared to the white race. The Native American led with an odd ratio of 1.431 (C.I: 1.261, 1.625) followed by Hispanic with 1.373 (C.I:1.320, 1.429). The Asian or Pacific Islander had an odd ratio of 1.313 (C.I: 1.216, 1.417), Blacks 1.300 (C.I: 1.1258, 1.344) and other races 1.290 (C.I: 1.190, 1.398).

Hyperlipidemia had an odds ratio of 1.239 (C.I: 1.207, 1.272) followed by hypercholesterolemia with odds ratio 1.199 (C.I: 1.145, 1.257), gender with odds ratio 1.179 (C.I: 1.149, 1.210), family history of diabetes with odds ratio 1.140 (C.I: 1.008,

1.289) and Hypertension with odds ratio 1.127 (C.I: 1.095, 1.159). All variables discussed above were significantly associated with Diabetes Type II with Ophthalmic Manifestations had a ratio of (p < 0.001) except the family history of diabetes with p < 0.05.

Table 14: Odds ratio estimates for DMT2 with ophthalmic manifestations

	Odds Ratio	p-value	95.0% C.I. for Odds Ratio	
			Lower	Upper
Gender [Female]	1.179	.000	1.149	1.210
White		.000		
Black	1.300	.000	1.258	1.344
Hispanic	1.373	.000	1.320	1.429
Asian or Pacific Islander	1.313	.000	1.216	1.417
Native American	1.431	.000	1.261	1.625
Other	1.290	.000	1.190	1.398
Family history of diabetes mellitus	1.140	.036	1.008	1.289
Obesity	.945	.000	.915	.975
Smoking	.644	.000	.610	.680
Alcohol related disorders	.641	.000	.580	.709
Hyperlipidemia	1.239	.000	1.207	1.272
Hypertension	1.127	.000	1.095	1.159
Hypercholesterolemia	1.199	.000	1.145	1.257
Hyperglyceridemia	.764	.003	.638	.915
Asthma	.895	.000	.853	.941
18-24		.000		
25-34	.926	.783	.537	1.597
35-49	1.110	.696	.657	1.875
50-64	1.163	.571	.690	1.962
65 and older	1.093	.740	.648	1.843

Variables with low odd ratios were obesity, smoking, alcohol related disorders, hyperglyceridemia and asthma. There were the variables that decreased the chance of getting Diabetes Type II with Ophthalmic Manifestations (see table 14). Obesity had the odds ratio 0.945 (C.I: 0.915, 0.975) followed by asthma with odds ratio 0.895 (C.I: 0.853, 0.941), hyperglyceridemia with odds ratio 0.764 (C.I: 0.638, 0.915), smoking with odds

ratio 0.644 (C.I: 0.610, 0.680) and alcohol related disorders with odds ratio 0.641 (C.I: 0.580, 0.709). For variables with lower odd ratios only the hyperglyceridemia variable had a ratio of ($p < 0.05$) while others had a ratio of ($p < 0.001$).
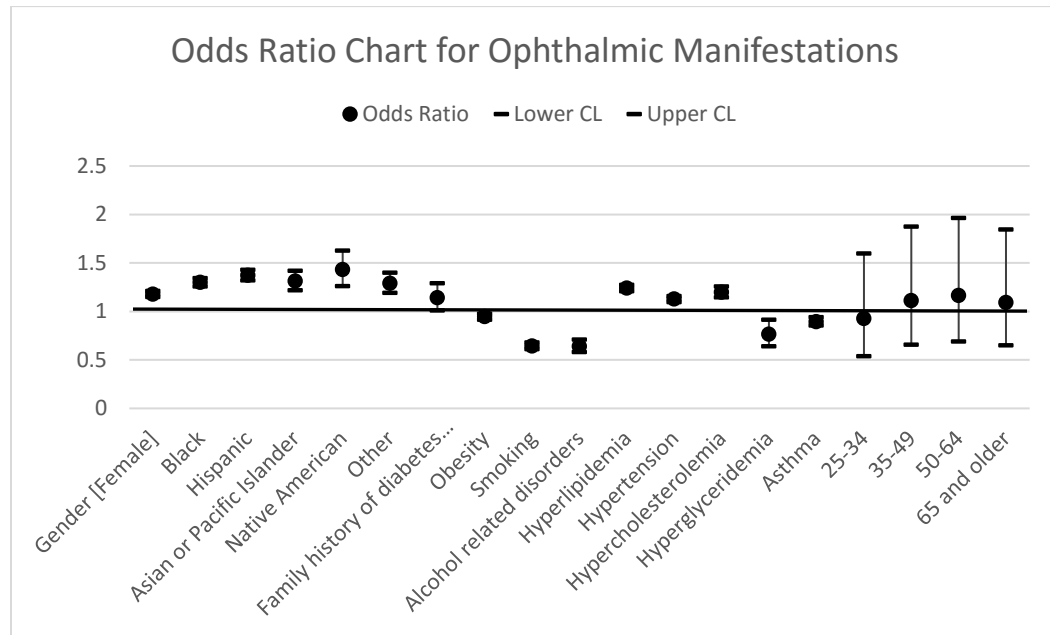
Figure 23: Odds ratio results chart for ophthalmic manifestations

4.6 Diabetes Type II with Complication Neurological Manifestations:

4.6.1 Descriptive Statistics

Data was collected from a total of 452,223 patients with diabetes type 2 with complications. Of these, 49.8% (225432) of the total patients were found to have Neurological Manifestations (see table 15). From all of the risk factors the highest numbers of cases of diabetes mellitus types 2 are from the patients who have Hyperlipidemia (40.5%), Hypertension (42.2%) and obesity (25.1%). Risk factors that have least number of cases of diabetes mellitus types 2 are from the patients who have Hypercholesterolemia (0.5%), Family History of diabetes (0.9) and Vitamin d deficiency (1.3%).

Table 15: Descriptive statistics for DMT2 with neurological manifestations

	Neurological	%	No Neurological	%	Total	%
Number of patient	225432	49.8%	226791	50.2%	452223	100%
Mean [SD] age	66.6[12.8]		68.07[12.65]		67.3[12.7]	
	N	%	N	%	N	%
Risk Factors						
Family History of diabetes	2020	0.9%	2081	0.9%	4101	0.9%
Obesity	56661	25.1%	42902	18.9%	99563	22.0%
Smoking	23463	10.4%	7499	3.3%	30962	6.8%
Alcohol	6626	2.9%	5593	2.5%	12219	2.7%
Hypertension	95145	42.2%	34243	15.1%	129388	28.6%
Hypercholesterolemia	17868	7.9%	15408	6.8%	33276	7.4%
Hyperglyceridemia	1617	0.7%	1311	0.6%	2928	0.6%
Vitamin d deficiency	3031	1.3%	3232	1.4%	6263	1.4%
Asthma	20337	9.0%	14447	6.4%	34784	7.7%
Hyperlipidemia	91274	40.5%	84612	37.3%	175886	38.8%

Young adults (18-24) who made up 0.1% of the total patients were least affected by diabetes type 2 with complication having 0.1% of this age group as affected by neurological. The group 50-64 years made up 31.2% of the data and this group had 32.9% of the patients diagnosed with neurological.
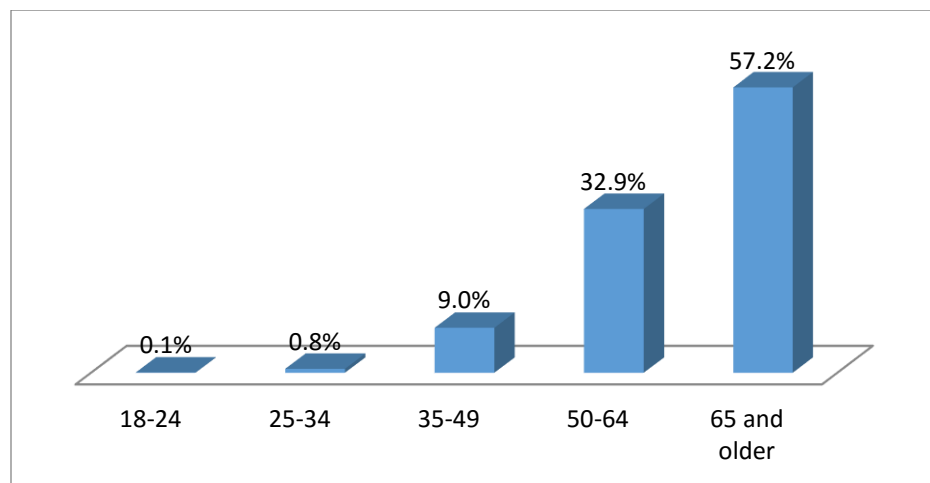
Figure 24: The age distribution of DMT2 with neurological patients

The group that had the highest number of patients diagnosed with neurological was the group 65 years and older of age with 57.2 percent of this age group having neurological. Thus the number of patients that had a high incidence of diabetes mellitus type 2 with neurological was above the age of 50 and this constituted 90.1% of the total number of patients that had diabetes mellitus type 2 with neurological.
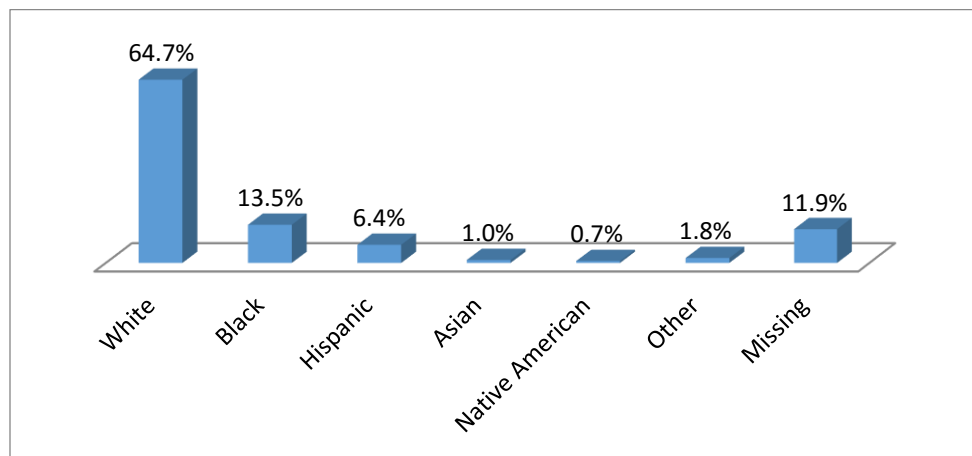
Figure 25: The race distribution of DMT2 with neurological patients

Whites who were the majority race had the highest figures of those with neurological at 64.7%. Native Americans, Hispanics, Asian and the missing ethnicity had low numbers with neurological. Black race constituted 16.3% of the total patients and 13.5% of these had diabetes mellitus type 2 with neurological Hispanics ethnicity also had a high incidence of diabetes mellitus type 2 with neurological which was at 6.4%. Native Americans had the least number of diabetes mellitus type 2 with complication patients at 0.8% of the total patients from the data and of these an even smaller number had neurological at 0.7%.
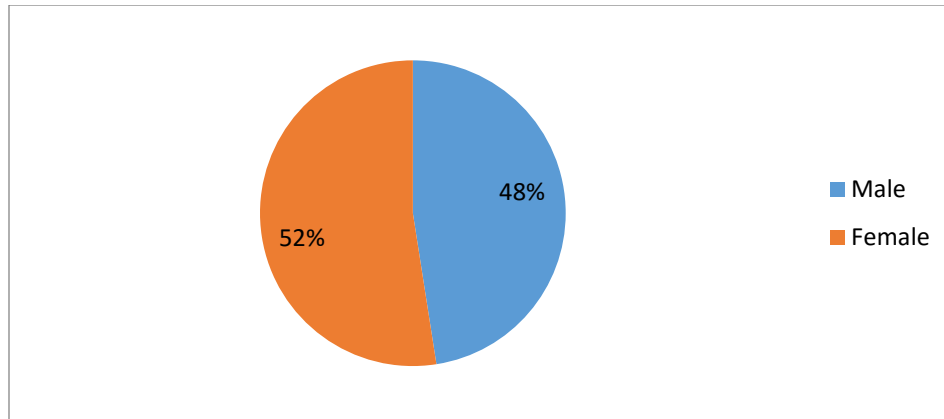
Figure 26: The gender distribution of DMT2 with neurological patients

Males and females were almost equally affected with neurological. Females represented 52% of the total patients and those affected by neurological and Males represented 48% of the total patients with diabetes type 2 with neurological. The difference between the female and male patients with neurological was 4% the male's figures being slightly lower.

4.6.2 Prevalence Rate of Neurological Manifestations Complication by Race

Figure 27 contains the prevalence rate for each race considered in this study. From the figure it was clear that Black ethnic group led with prevalence rate close to the 87 per 100,000 persons followed by the ethnic group White with prevalence rate close to 69 per 100,000 person. Native American ethnic group had prevalence rate of 60 per 100,000 person, Hispanic ethnic group had prevalence rate of 40 per 100,000 person and Asian had the lowest prevalence rate of all close to 23 per 100,000. It indicated that a person belong to Black ethnic group was more likely to have Diabetes Type II with Neurological Manifestations and Asian people were the least likely to have that disease.

137
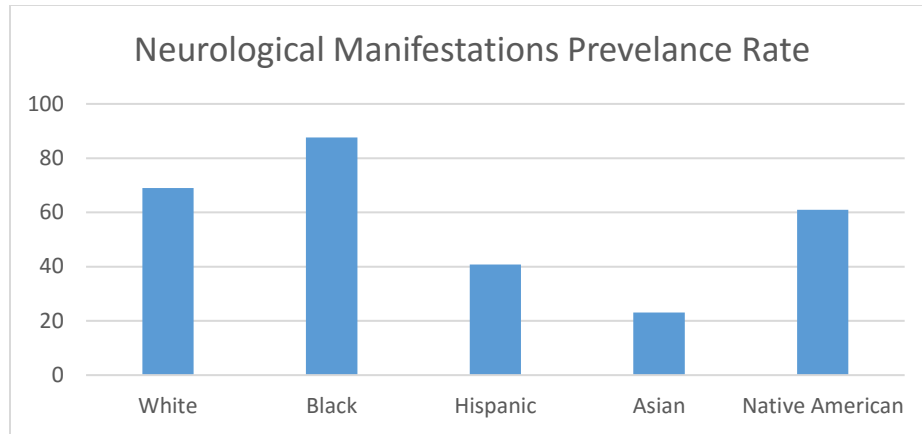
Figure 27: Prevalence rate by race for neurological manifestations

4.6.3 Analysis of Risk Factors for Diabetes Type II with Neurological Manifestations

In order to analyze the risk factors for the Diabetes Type II with Neurological Manifestations, binary logistic regression analysis is used. The same risk factors are considered as above. Logistic regression model assisted to identify that which independent variable is significant in predicting the dependent variable that is Diabetes Type II with Neurological Manifestations.

4.6.3.1. Dependent variable: Diabetes Type II with Neurological Manifestations

In sample data total 225432 patients' diagnoses as the Diabetes Type II with Neurological Manifestations out of 452232. The dependent variable, Diabetes Type II with Neurological Manifestations is treated in a same way as previous. Both of the genders are considered for this with age 18 and above. The table 16 given below contains all the important information about the significance of the independent variables.

4.6.3.2 Significance of Independent Variables in the Model

All variables given in table 16 were significantly related with Diabetes Type II with Neurological Manifestations, $p < 0.001$, except one category of age, $p > 0.05$. Alcohol related disorder and Hypercholesterolemia was not included in the model because they was

not strongly associated with Diabetes Type II with Neurological Manifestations. All the variables had different odds ratios and variables with higher odd ratios had increases chances of developing Diabetes Type II with Neurological Manifestations.

Table 16: Odds ratio estimates for DMT2 with neurological manifestations

| | Odds Ratio | p-value | 95.0% C.I. for Odds Ratio | |
			Lower	Upper
Gender [Female]	1.162	.000	1.146	1.177
White		.000		
Black	.566	.000	.556	.576
Hispanic	.421	.000	.412	.431
Asian or Pacific Islander	.285	.000	.272	.300
Native American	.614	.000	.571	.659
Other	.617	.000	.591	.645
Family history of Diabetes	.841	.000	.785	.901
Obesity	1.200	.000	1.181	1.220
Smoking	1.143	.000	1.115	1.171
Hyperlipidemia	.975	.000	.962	.989
Hypertension	3.800	.000	3.741	3.859
Hyperglyceridemia	.881	.003	.810	.957
Asthma	1.256	.000	1.224	1.288
Vitamin D deficiency	.932	.014	.880	.986
18-24		.000		
25-34	1.486	.005	1.130	1.955
35-49	1.682	.000	1.290	2.193
50-64	1.473	.004	1.131	1.919
65 and older	1.230	.125	.944	1.602

Variables age, gender, hypertension, obesity, smoking, and Asthma indicated higher odds ratios and hence increased the chances of getting Diabetes Type II with Neurological Manifestations. Hypertension had the highest odds ratio 3.800 (C.I: 3.741, 3.859), indicating that patient with hypertension had 3.8 times increased chances to get Diabetes Type II with Neurological Manifestations. All participating age groups had

heightened levels of developing Diabetes Type II with Neurological Manifestations when compared to the 18-24 years old. Age group 35-49 led with an odd ratio of 1.682 (C.I: 1.290, 2.193) followed by age group 25-34 with 1.486 (C.I:1.130, 1.955) and 50-64 with odds ratio 1.473 (C.I: 1.131, 1.919).

Asthma had an odds ratio of 1.256 (C.I: 1.224, 1.288) followed by obesity with odds ratio 1.200 (C.I: 1.181, 1.220), gender with odds ratio 1.162 (C.I: 1.146, 1.177) and smoking with odds ratio 1.143 (C.I: 1.115, 1.171). All variables discussed above were significantly associated with Diabetes Type II with Neurological Manifestations had a ratio of ($p < 0.001$) except the age with $p < 0.05$.

Variables with low odd ratios were ethnicity, family history of diabetes, hyperlipidemia, hyperglyceridemia and vitamin d deficiency. These were the variables that decreased the chance of getting Diabetes Type II with Neurological Manifestations. Hyperlipidemia had the odds ratio 0.975 (C.I: 0.962, 0.989) followed by vitamin d deficiency with odds ratio 0.932 (C.I: 0.880, 0.986), hyperglyceridemia with odds ratio 0.881 (C.I: 0.810, 0.957), family history of diabetes with odds ratio 0.841 (C.I: 0.785, 0.901). Ethnicity had reduced the chances of getting Diabetes Type II with Neurological Manifestations, other led with odds ratio 0.617 (C.I: 0.591, 0.645) followed by Native American with the odds ratio 0.614 (C.I: 0.571, 0.659), Black with odds ratio 0.566 (C.I: 0.556, 0.576), Hispanic with odds ratio 0.421 (C.I: 0.412, 0.431) and Asian or Pacific Islander with odds ratio 0.285 (C.I: 0.272, 0.300). For variables with lower odd ratios only the hyperglyceridemia and vitamin d deficiency variable had a ratio of ($p < 0.05$) while others had a ratio of ($p < 0.001$).
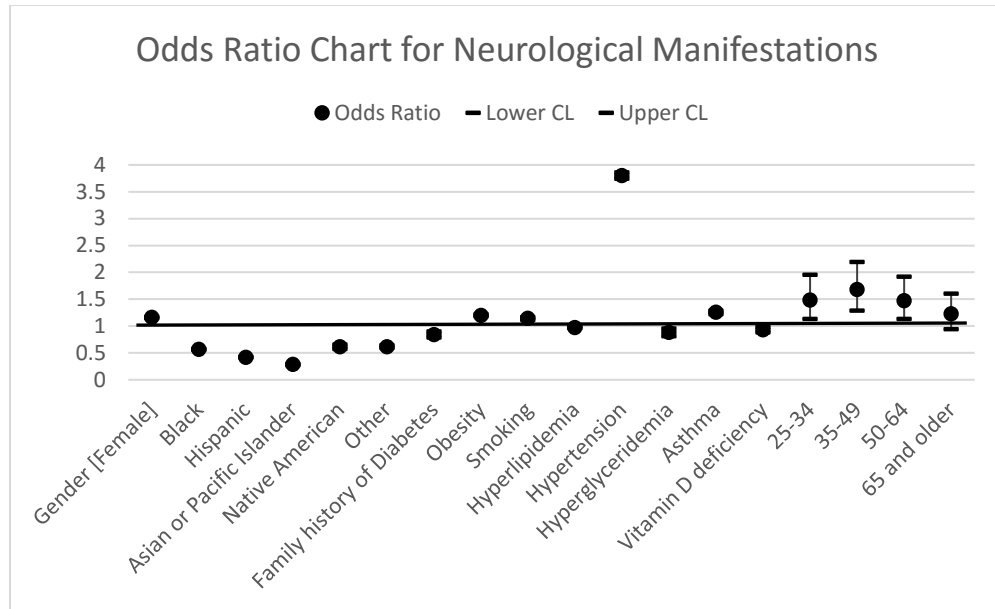
Figure 28: Odds ratio results chart for neurological manifestations

4.7 Diabetes Type II with Complication Peripheral Circulatory Disorders:

4.7.1 Descriptive Statistics

Data was collected from a total of 452,223 patients with diabetes type 2 with complications. Of these, 6.7% (30428) of the total patients were found to have peripheral circulatory disorders (see table 17). From all of the risk factors the highest numbers of cases of diabetes mellitus types 2 are from the patients who have Hyperlipidemia (32.4%), Hypertension (32.2%) and obesity (14%). Risk factors that have least number of cases of diabetes mellitus types 2 are from the patients who have Hypercholesterolemia (0.3%), Vitamin d deficiency (0.7%) and Family History of diabetes (0.9%).

Young adults (18-24) who made up 0.1% of the total patients were least affected by diabetes type 2 with complication having 0.0% of this age group as affected by peripheral. The group 50-64 years made up 31.2% of the data and this group had 29.1% of the patients diagnosed with peripheral.

Table 17: Descriptive statistics for DMT2 with peripheral circulatory disorders

	Peripheral	%	No Peripheral	%	Total	
Number of patient	30428	6.7%	421795	93.3%	452223	100%
Mean [SD] age	69.2[12.3]		67.2[12.8]		67.3[12.7]	
	N	%	N	%	N	%
Risk Factors						
Family History of diabetes	262	0.9%	3839	0.9%	4101	0.9%
Obesity	4246	14.0%	95317	22.6%	99563	22.0%
Smoking	2786	9.2%	28176	6.7%	30962	6.8%
Alcohol	669	2.2%	11550	2.7%	12219	2.7%
Hypertension	9807	32.2%	119581	28.4%	129388	28.6%
Hypercholesterolemia	2095	6.9%	31181	7.4%	33276	7.4%
Hyperglyceridemia	88	0.3%	2840	0.7%	2928	0.6%
Vitamin d deficiency	212	0.7%	6051	1.4%	6263	1.4%
Asthma	1254	4.1%	33530	7.9%	34784	7.7%
Dyslipidemia	9847	32.4%	166039	39.4%	171787	38.0%

The group that had the highest number of patients diagnosed with peripheral was the group 65 years and older of age with 64.8 percent of this age group having peripheral. Thus the number of patients that had a high incidence of diabetes mellitus type 2 with peripheral was above the age of 50 and this constituted 93.9% of the total number of patients that had diabetes mellitus type 2 with peripheral.
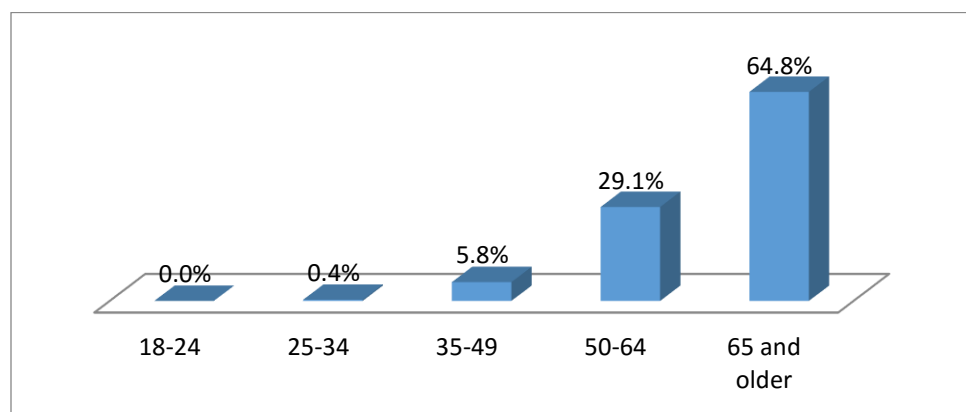
Figure 29: The age distribution of DMT2 with peripheral circulatory disorders patients

Whites who were the majority race had the highest figures of those with peripheral at 53.9%. Native Americans, Hispanics, Asian and the missing ethnicity had low numbers with peripheral. Black race constituted 16.3% of the total patients and 19.2% of these had diabetes mellitus type 2 with peripheral Hispanics ethnicity also had a high incidence of diabetes mellitus type 2 with peripheral which was at 13.8%. Native Americans had the least number of diabetes mellitus type 2 with complication patients at 0.8% of the total patients from the data and of these an even smaller number had peripheral at 0.7%.
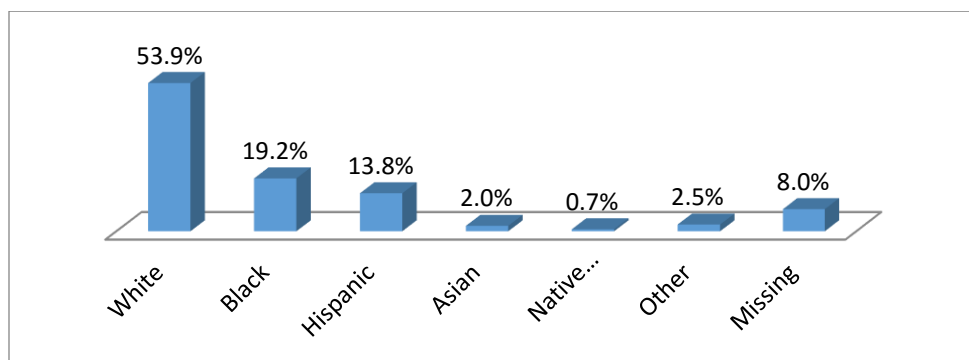
Figure 30: The race distribution of dmt2 with peripheral circulatory disorders patients

Males and females were almost equally affected with peripheral. Males represented 60% of the total patients and those affected by peripheral and Females represented 40% of the total patients with diabetes type 2 with peripheral. The difference between the female and male patients with peripheral was 10% the female's figures being low.
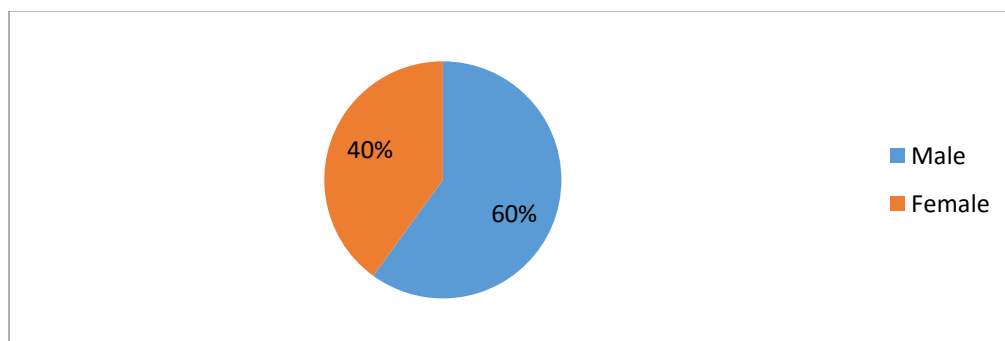
Figure 31: The gender distribution of dmt2 with peripheral circulatory disorders patients

4.7.2 Prevalence Rate of Peripheral Circulatory Disorders Complication by Race

Figure 32 contains the prevalence rate for each race considered in this study. From the figure it was clear that Black ethnic group led with prevalence rate close to the 16.8 per 100,000 persons followed by the ethnic group Hispanic with prevalence rate close to 11.8 per 100,000 person. Native American ethnic group had prevalence rate of 8.8 per 100,000 person, White ethnic group had prevalence rate of 7.7 per 100,000 person and Asian had the lowest prevalence rate of all close to 5.8 per 100,000. It indicated that a person belong to Black ethnic group was more likely to have Diabetes Type II with Peripheral Circulatory Disorders and Asian people were the least likely to have that disease.
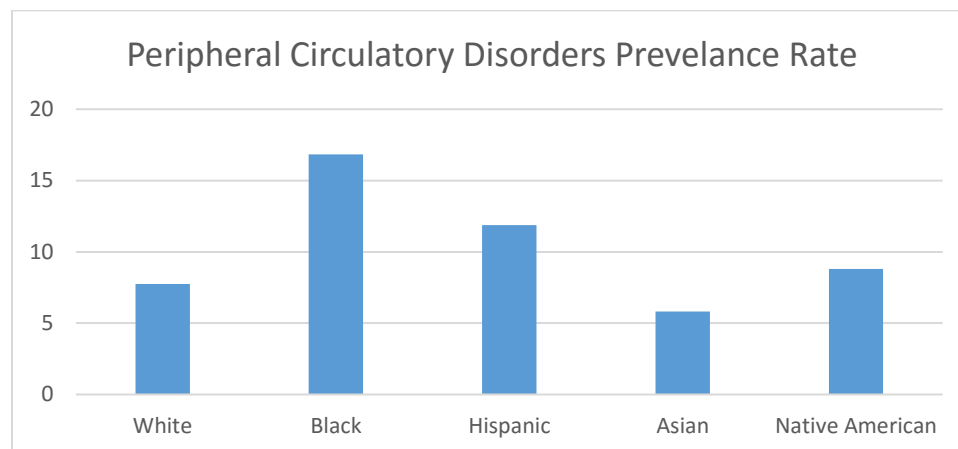
Figure 32: Prevalence rate by race for peripheral circulatory disorders

4.7.3 Analysis of Risk Factors for Diabetes Type II with Peripheral Circulatory Disorders

In order to analyze the risk factors for the Diabetes Type II with Peripheral Circulatory Disorders, binary logistic regression analysis is used. The same risk factors are considered as for the previous. Logistic regression model assisted to identify that which

144

independent variable is significant in predicting the dependent variable that is Diabetes Type II with Peripheral Circulatory Disorders.

4.7.3.1. Dependent variable: Diabetes Type II with Peripheral Circulatory Disorders

In sample data total 30428 patients' diagnoses as the Diabetes Type II with Peripheral Circulatory Disorders out of 452232. The dependent variable that is binary is treated in the same way as the previous dependent variables. The table 18 given below contains all the important information about the significance of the independent variables.

4.7.3.2 Significance of Independent Variables in the Model

All variables given in table 18 were significantly related with Diabetes Type II with Peripheral Circulatory Disorders, $p < 0.001$, except two categories of ethnic group, $p > 0.05$. Family history of diabetes was not included in the model because it was not strongly associated with Diabetes Type II with Peripheral Circulatory Disorders. All the variables had different odds ratios and variables with higher odd ratios had increases chances of developing Diabetes Type II with Peripheral Circulatory Disorders.

Variables age, smoking, hypertension and ethnic groups (excluding Asian or Pacific Islander and Native American) indicated higher odds ratios and hence increased the chances of getting Diabetes Type II with Peripheral Circulatory Disorders. Age groups had the highest odds ratio as all participating age groups had heightened levels of developing Diabetes Type II with Peripheral Circulatory Disorders when compared to the 18-24 years old. Age group 65 and older led with an odd ratio of 22.081 (C.I: 3.096, 41.066) followed by age group 50-64 with 18.560 (C.I: 2.602, 34.518), age group 35-49 with odds ratio 13.648 (C.I: 1.913, 25.838) and 25-34 years old with odds ratio 7.994 (C.I: 1.110, 14.878).

Table 18: Odds ratio estimates for DMT2 with peripheral circulatory disorders

	Odds Ratio	p-value	95.0% C.I. for Odds Ratio	
			Lower	Upper
Gender [Female]	.656	.000	.640	.673
White		.000		
Black	1.463	.000	1.417	1.510
Hispanic	1.749	.000	1.687	1.813
Asian or Pacific Islander	.968	.459	.890	1.054
Native American	1.143	.060	.995	1.313
Other	1.350	.000	1.250	1.458
Obesity	.628	.000	.606	.650
Smoking	1.125	.000	1.076	1.176
Alcohol related disorders	.650	.000	.598	.707
Hyperlipidemia	.712	.000	.693	.731
Hypertension	1.469	.000	1.430	1.509
Hypercholesterolemia	.836	.000	.796	.877
Hyperglyceridemia	.498	.000	.400	.621
Asthma	.582	.000	.548	.618
Vitamin D deficiency	.526	.000	.455	.607
18-24		.000		
25-34	7.994	.039	1.110	14.878
35-49	13.648	.009	1.913	25.838
50-64	18.560	.004	2.602	34.518
65 and older	22.081	.002	3.096	41.066

Ethic groups had the second highest odds ratio where Hispanic led with 1.749 (C.I: 1.687, 1.813) followed by black with odds ratio 1.463 (C.I: 1.417, 1.510) and other with odds ratio 1.350 (C.I: 1.250, 1.458). Hypertension had the odds ratio 1.469 (C.I: 1.430, 1.509), indicating that patient with hypertension had 1.469 times increased chances to get Diabetes Type II with Peripheral Circulatory Disorders. Smoking had the odds ratio 1.125 (C.I: 1.076, 1.176) indicating that smokers had higher chances to attain Diabetes Type II with Peripheral Circulatory Disorders. Out of all variables discussed above were

significantly associated with Diabetes Type II with Peripheral Circulatory Disorders had a ratio of ($p < 0.001$) except the age with $p < 0.05$.

Variables with low odd ratios were gender, Obesity, alcohol related disorders, hyperlipidemia, hypercholesterolemia, hyperglyceridemia, asthma and vitamin d deficiency. These were the variables that decreased the chance of attaining Diabetes Type II with Peripheral Circulatory Disorders. Hypercholesterolemia had the odds ratio 0.836 (C.I: 0.796, 0.877) followed by gender with odds ratio 0.656 (C.I: 0.640, 0.673) indicating that male were more likely to get Diabetes Type II with Peripheral Circulatory Disorders, alcohol related disorders with odds ratio 0.650 (C.I: 0.598, 0.707), obesity with odds ratio 0.628 (C.I: 0.606, 0.650).

Asthma had the odds ratio of 0.580 (C.I: 0.548, 0.618) followed by vitamin d deficiency with the odds ratio 0.526 (C.I: 0.455, 0.607) and hyperglyceridemia with odds ratio 0.498 (C.I: 0.400, 0.621). All the variables with lower odd ratios are significantly associated with Diabetes Type II with Peripheral Circulatory Disorders with ($p < 0.001$).
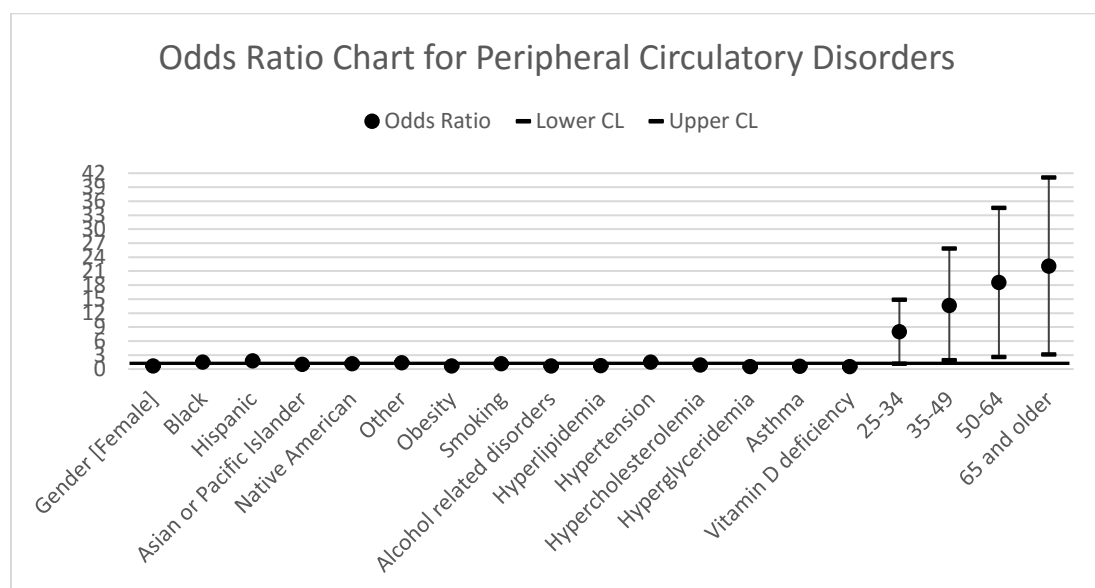
Figure 33: Odds ratio results chart for peripheral circulatory disorders

4.8. Binary Logistic Regression Classification Model

In order to classify a patient, into being diabetic with type II or not for given complication, binary logistic regression is used. An estimate of the probability, for a person being or not being diabetic with type II, is calculated based on the independent variables included in the model. So the Logistic regression is applied for all the six complications and given below.

4.8.1. For Diabetes Type II with Ketoacidosis:

The table 19 the confusion matric is given, where cells on the main diagonal are correct predictions and Cells off the diagonal are incorrect predictions. So of the cases used to create the model, all the people (392,417) who previously did not have Diabetes Type II with Ketoacidosis are classified correctly. The model accuracy is approximately 97.1% which gives us an idea that misclassification rate will be less than 3%. This is an indication that model is a good fit.

Table 19: Classification table for DMT2 with ketoacidosis

Observed	Predicted Diabetes with ketoacidosis No	Yes	Percentage Correct
Diabetes Type II No with ketoacidosis	392417	28	100.0
Yes	11620	26	.2
Overall Percentage			97.1
a. The cut value is .500			

The Receiver Operating Characteristic (ROC) curve given in the Figure 33 where diagonal line is the cutoff point that is 0.50. The figure 34 shows that area under the curve (AUC) is around 0.71. So this AUC value is acceptable since it is higher than random classifier that is 0.50.

Figure 34: Binary logistic regression ROC curve for DMT2 with ketoacidosis

4.8.2. For Diabetes Type II with Hyperosmolarity:

The table 20 the confusion matric is given, so of the cases used to create the model, all the people (398,191) who previously did not have Diabetes Type II with hyperosmolarity are classified correctly. The model accuracy is approximately 98.5% which gives us an idea that misclassification rate will be less than 2%. This is an indication that model is a good fit.

Table 20: Classification table for DMT2 with hyperosmolarity

	Predicted		
	Diabetes with hyperosmolarity		Percentage Correct
Observed	No	Yes	
Diabetes Type II with hyperosmolarity No	398191	0	100.0
Yes	5900	0	.0
Overall Percentage			98.5

The Receiver Operating Characteristic (ROC) curve given in the Figure 28 where diagonal line is the cutoff point that is 0.50. The figure 35 shows that area under the curve (AUC) is around 0.65. So this AUC value is acceptable since it is higher than random classifier that is 0.50.

Figure 35: Binary logistic regression ROC curve for DMT2 with hyperosmolarity

4.8.3 For Diabetes Type II with Renal Manifestations:

The table 21 have classification table, so of the cases used to create the model, all the people who previously did not have Diabetes Type II with renal manifestations, 245,556 are classified correctly. While all the people who previously did have Diabetes Type II with renal manifestations, 31,483 are classified correctly. The model accuracy is approximately 68.6% this is an indication that model is a good fit.

Table 21: Classification table for DMT2 with renal manifestations

		Predicted		
		Diabetes with renal manifestations		Percentage
Observed		No	Yes	Correct
Diabetes Type II with renal manifestations	No	245556	24059	91.1
	Yes	102993	31483	23.4
Overall Percentage				68.6

The Receiver Operating Characteristic (ROC) curve for this model is given in the Figure 36. The curve shows that area under the curve (AUC) is around 0.72. So this AUC value is acceptable since it is higher than random classifier that is 0.50. These same information is give in the Table 21.
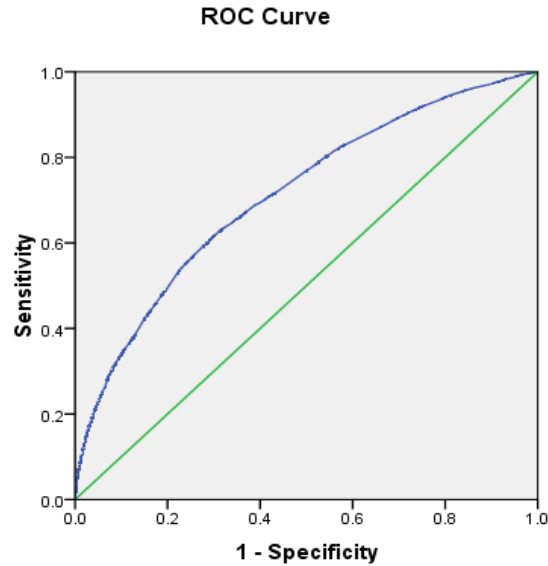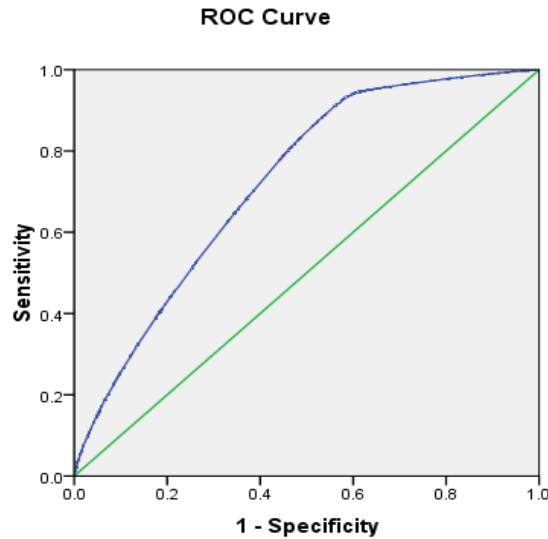
Figure 36: Binary Logistic Regression ROC Curve for DMT2 with renal manifestations

4.8.4. For Diabetes Type II with Ophthalmic Manifestations:

The table 22 have classification table, so of the cases used to create the model, all the people (378559) who previously did not have Diabetes Type II with ophthalmic manifestations, are all classified correctly. While all the people (25532) who previously did have Diabetes Type II with ophthalmic manifestations, are all misclassified. The model accuracy is approximately 93.7% this is an indication that model is a good fit.

Table 22: Classification table for DMT2 ophthalmic manifestations

		Predicted		
		Diabetes with ophthalmic manifestations		Percentage Correct
Observed		No	Yes	
Diabetes Type II with ophthalmic manifestations	No	378559	0	100.0
	Yes	25532	0	.0
Overall Percentage				93.7

The Receiver Operating Characteristic (ROC) curve for this model is given in the Figure 37. The curve shows that area under the curve (AUC) is around 0.56. So this AUC value is acceptable since it is higher than random classifier that is 0.50.
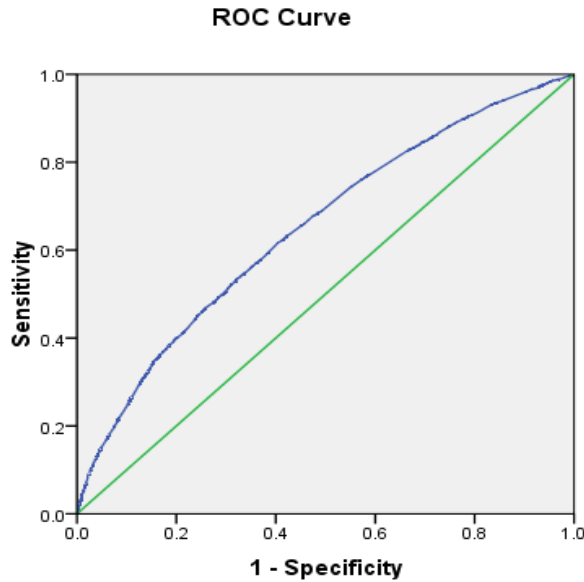

Figure 37: Binary logistic regression ROC curve for DMT2 with ophthalmic manifestations

4.8.5. For Diabetes Type II with Neurological Manifestations:

The table 23 have classification table, so of the cases used to create the model, all the people who previously did not have Diabetes Type II with neurological manifestations, 164,511 of them are classified correctly. While all the people who previously did have Diabetes Type II with neurological manifestations 95,457 of them are classified correctly. The model accuracy is approximately 64.3% this is an indication that model is a good fit.

Table 23: Classification table for DMT2 with neurological manifestations

Observed	Predicted		Percentage Correct
	Diabetes with Neurological manifestations		
	No	Yes	
Diabetes Type II with No	164511	41029	80.0
Neurological manifestations Yes	103094	95457	48.1
Overall Percentage			64.3

The Receiver Operating Characteristic (ROC) curve for this model is given in the Figure 38. The curve shows that area under the curve (AUC) is around 0.69. So this AUC value is acceptable since it is higher than random classifier that is 0.50.
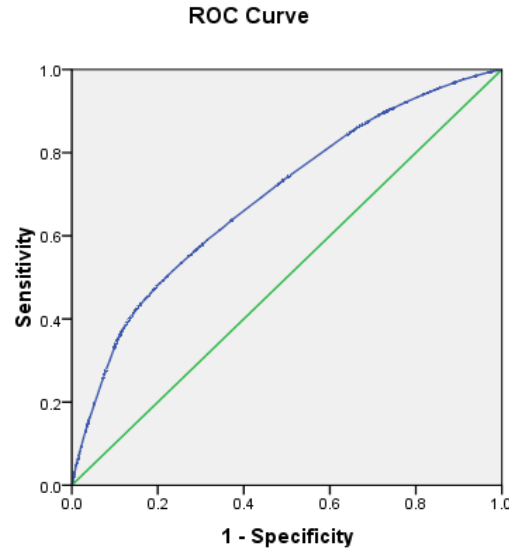
Figure 38: Binary logistic regression ROC curve for DMT2 with neurological manifestations

4.8.6 For Diabetes Type II with Peripheral Circulatory Disorders:

The table 24 have classification table, so of the cases used to create the model, all the people (376105) who previously did not have Diabetes Type II with neurological manifestations, are classified correctly. While all the people (27986) who previously did have Diabetes Type II with neurological manifestations are misclassified. The model accuracy is approximately 93.1% this is an indication that model is a good fit.

Table 24: Classification table for DMT2 with peripheral circulatory disorders

		Predicted		
		Diabetes with peripheral circulatory disorders		Percentage Correct
Observed		No	Yes	
Diabetes Type II with peripheral circulatory disorders	No	376105	0	100.0
	Yes	27986	0	.0
Overall Percentage				93.1

The Receiver Operating Characteristic (ROC) curve for this model is given in the Figure 39. The curve shows that area under the curve (AUC) is around 0.62. So this AUC value is acceptable since it is higher than random classifier that is 0.50.
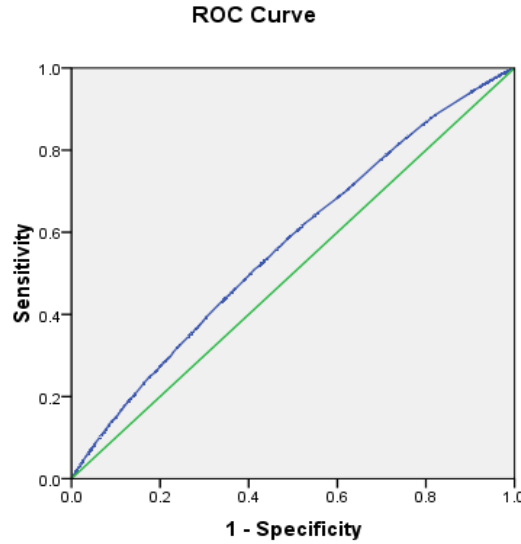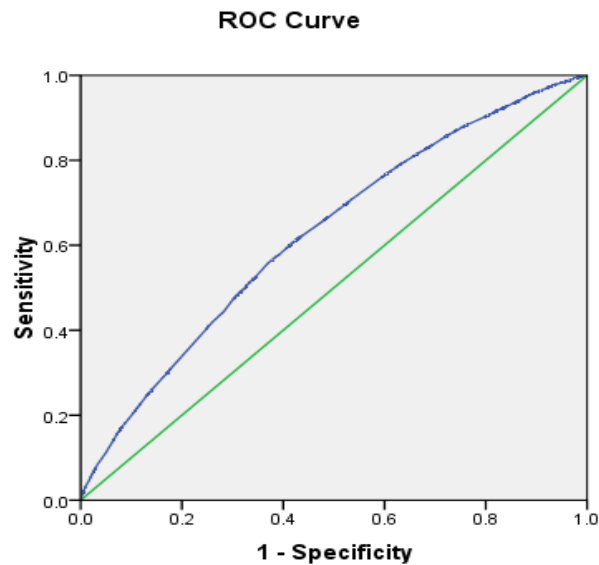
ROC Curve

Figure 39: Binary Logistic Regression ROC Curve for DMT2 with peripheral circulatory disorders

4.9. Multilayer Perceptron Neural Network Classification Model

In order to classify a patient, into being diabetic with type II or not, for given complication, multilayer perceptron neural network is used. An estimate of the probability, for a person being or not being diabetic with type II, is calculated based on the independent variables Gender (male, female), Race (white, Black, Hispanic, Asian or Pacific Islander, Native American and other), family history of diabetes, obesity, smoking, alcohol related disorders, dyslipidemia, Hypertension, Hypercholesterolemia, Asthma, Vitamin D deficiency and age. So the multilayer perceptron neural network model is applied for all the six complications and given below.

4.9.1. For Diabetes Type II with Ketoacidosis:

The Multilayer perceptron (ANN) for diabetes type II with ketoacidosis, 70% of the data is used for training, 15% is used for testing and 15% is used for validation (holdout sample). The classification table given in table 25 shows the model accuracy rate and misclassification rate for training, testing and holdout sample. The training, testing and hold out sample have 97.1% of accuracy rate. Overall models misclassification rate is less than 3%.

Table 25: AAN classification table for DMT2 with ketoacidosis

Sample	Observed	Predicted		
		No	Yes	Percent Correct
	No	275109	1	100.0%
Training	Yes	8167	0	.0%
	Overall Percent	100.0%	0.0%	97.1%
	No	58695	0	100.0%
Testing	Yes	1747	0	.0%
	Overall Percent	100.0%	.0%	97.1%
	No	58640	0	100.0%
Holdout	Yes	1732	0	.0%
	Overall Percent	100.0%	.0%	97.1%
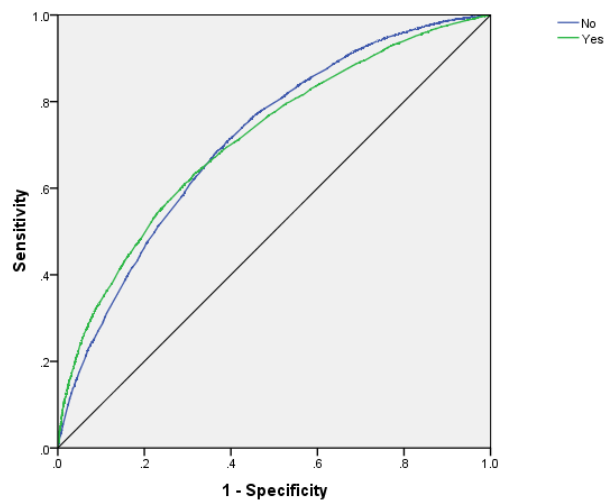
Figure 40: Multilayer perceptron ANN ROC curve for DMT2 with ketoacidosis

The Receiver Operating Characteristic (ROC) curve for this model is given in the Figure 40. The curve shows that area under the curve (AUC) is around 0.70. So this AUC value is acceptable since it is higher than random classifier that is 0.50.

4.9.2. For Diabetes Type II with Hyperosmolarity:

The Multilayer perceptron (ANN) for diabetes type II with hyperosmolarity, the same percentage of sample is used for training, testing and validation (holdout sample). The classification table given in table 26 shows the model accuracy rate and misclassification rate for training, testing and holdout sample.

Table 26: ANN classification table for DMT2 with hyperosmolarity

Sample	Observed	Predicted No	Yes	Percent Correct
Training	No	279104	0	100.0%
	Yes	4173	0	.0%
	Overall Percent	100.0%	.0%	98.5%
Testing	No	59547	0	100.0%
	Yes	895	0	.0%
	Overall Percent	100.0%	.0%	98.5%
Holdout	No	59540	0	100.0%
	Yes	832	0	.0%
	Overall Percent	100.0%	.0%	98.6%

The training and testing sample have 98.5% of accuracy rate while the holdout sample have the 98.6% of the model accuracy. Overall models misclassification rate is less than 2%. The Receiver Operating Characteristic (ROC) curve for this model is given in the Figure 41. The curve shows that area under the curve (AUC) is around 0.61. So this AUC value is acceptable since it is higher than random classifier that is 0.50.
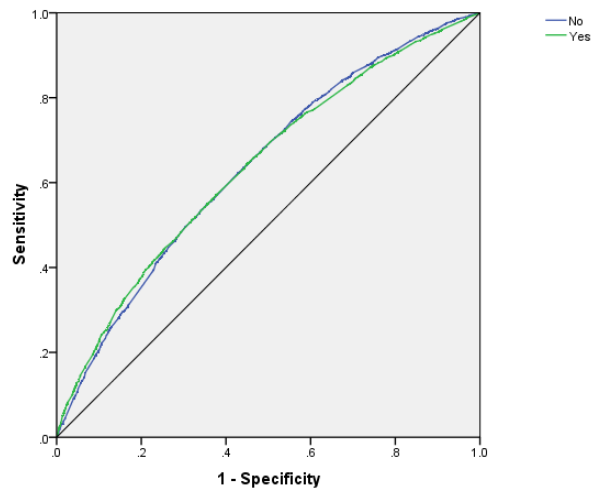
Figure 41: Multilayer perceptron ANN ROC Curve for DMT2 with hyperosmolarity

4.9.3. For Diabetes Type II with Renal Manifestations:

The Multilayer perceptron (ANN) for diabetes type II with renal manifestations and the same percentage of sample is used for training, testing and validation (holdout sample).

Table 27: ANN classification table for DMT2 with renal manifestations

Sample	Observed	Predicted No	Yes	Percent Correct
Training	No	174180	14436	92.3%
	Yes	75077	19140	20.3%
	Overall Percent	88.1%	11.9%	68.4%
Testing	No	37611	3105	92.4%
	Yes	16197	4128	20.3%
	Overall Percent	88.2%	11.8%	68.4%
Holdout	No	37230	3053	92.4%
	Yes	15947	3987	20.0%
	Overall Percent	88.3%	11.7%	68.4%

The classification table given in table 27 shows the model accuracy rate and misclassification rate for training, testing and holdout sample. Overall training, testing and holdout sample have the same percentage of correct predictions and that is 68.4%. Overall

models misclassification rate is less than 35%. The Receiver Operating Characteristic (ROC) curve for this model is given in the Figure 42. The curve shows that area under the curve (AUC) is around 0.70. So this AUC value is acceptable since it is higher than random classifier that is 0.50.

Figure 42: Multilayer Perceptron ANN ROC Curve for DMT2 with Renal Manifestations

4.9.4. For Diabetes Type II with Ophthalmic Manifestations:

The Multilayer perceptron (ANN) for diabetes type II with ophthalmic manifestations. The classification table given in table 28 shows the model accuracy rate and misclassification rate for training, testing and holdout sample. The training and holdout sample have 93.7% model accuracy and the testing sample have 93.6% of model accuracy rate. Overall models misclassification rate is less than 7%. The Receiver Operating Characteristic (ROC) curve for this model is given in the Figure 43. The curve shows that area under the curve (AUC) is around 0.56. So this AUC value is acceptable since it is higher than random classifier that is 0.50.

Table 28: ANN classification table for DMT2 ophthalmic manifestations

Sample	Observed	Predicted No	Yes	Percent Correct
	No	265035	0	100.0%
Training	Yes	17890	0	.0%
	Overall Percent	100.0%	.0%	93.7%
	No	56734	0	100.0%
Testing	Yes	3855	0	.0%
	Overall Percent	100.0%	.0%	93.6%
	No	56790	0	100.0%
Holdout	Yes	3787	0	.0%
	Overall Percent	100.0%	.0%	93.7%

Figure 43: Multilayer perceptron ANN ROC curve for DMT2 with ophthalmic manifestations

4.9.5. For Diabetes Type II with Neurological Manifestations:

The Multilayer perceptron (ANN) for diabetes type II with neurological manifestations and the classification table given in table 29 shows the model accuracy rate and misclassification rate for training, testing and holdout sample. The training sample have 64.2% testing sample have 64.4% and the holdout sample have the 64.3% of the model accuracy. Overall models misclassification rate is less than 36%.

159

Table 29: ANN classification table for DMT2 with neurological manifestations

Sample	Observed	Predicted No	Yes	Percent Correct
Training	No	111309	32581	77.4%
	Yes	68677	70481	50.6%
	Overall Percent	63.6%	36.4%	64.2%
Testing	No	24105	6870	77.8%
	Yes	14750	14965	50.4%
	Overall Percent	64.0%	36.0%	64.4%
Holdout	No	23805	6870	77.6%
	Yes	14681	14997	50.5%
	Overall Percent	63.8%	36.2%	64.3%
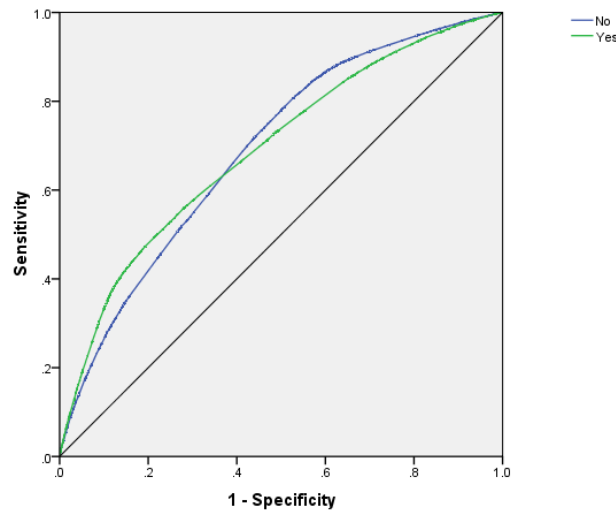
Dependent Variable: Diabetes with neurological manifestations

Figure 44: Multilayer Perceptron ANN ROC Curve for DMT2 with Neurological Manifestations

The Receiver Operating Characteristic (ROC) curve for this model is given in the Figure 44. The curve shows that area under the curve (AUC) is around 0.70. So this AUC value is acceptable since it is higher than random classifier that is 0.50.
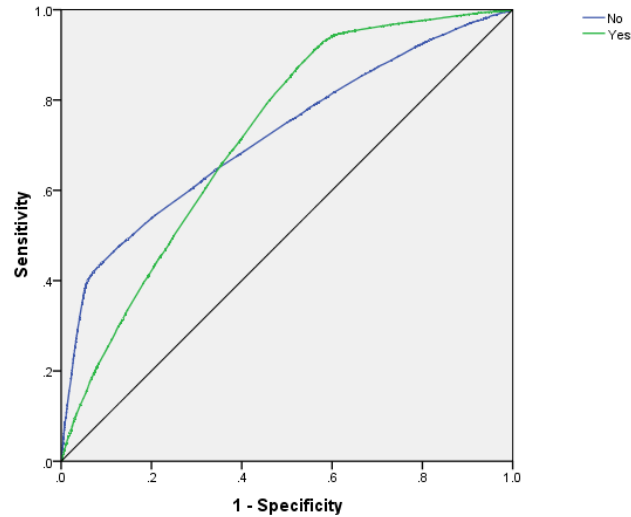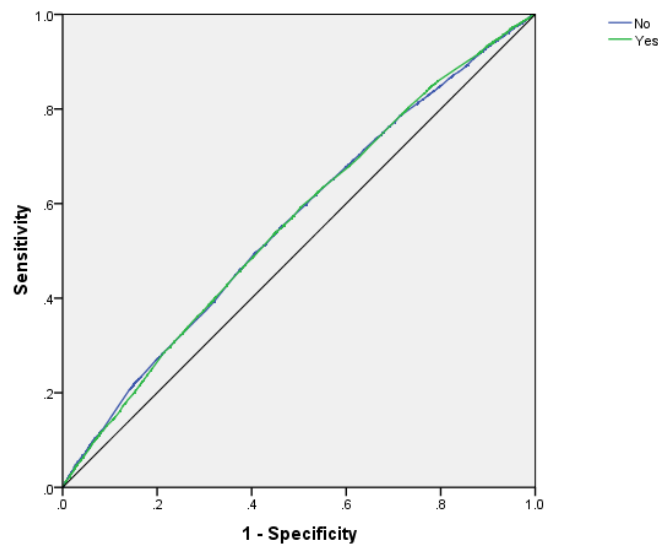
4.9.6. For Diabetes Type II with Peripheral Circulatory Disorders:

The Multilayer perceptron (ANN) for diabetes type II with peripheral circulatory disorders and classification table given in table 30 shows the model accuracy rate and

misclassification rate for training, testing and holdout sample. The training testing and

holdout sample have 93.1% model accuracy. Overall models misclassification rate is less

than 3%.

Table 30: ANN classification table for DMT2 with peripheral circulatory disorders

Sample	Observed	Predicted		
		No	Yes	Percent Correct
	No	263712	7	100.0%
Training	Yes	19675	0	.0%
	Overall Percent	100.0%	.0%	93.1%
	No	56297	0	100.0%
Testing	Yes	4147	0	.0%
	Overall Percent	100.0%	.0%	93.1%
	No	56096	1	100.0%
Holdout	Yes	4147	0	.0%
	Overall Percent	100.0%	.0%	93.1%

The Receiver Operating Characteristic (ROC) curve for this model is given in the Figure

45. The curve shows that area under the curve (AUC) is around 0.60. So this AUC value

is acceptable since it is higher than random classifier that is 0.50.
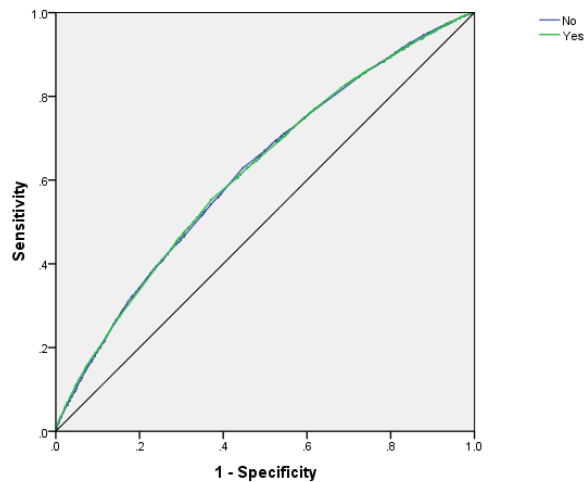
Figure 45: Multilayer Perceptron ANN ROC Curve for DMT2 with Peripheral Circulatory Disorders

CHAPTER V

V. DISCUSSION

5.1 Diabetes-Associated Complications and Their Connection with Risk Factors

The present study focused on the most widespread complications of type 2 diabetes, such as ketoacidosis, hyperosmolarity, renal manifestations, ophthalmic manifestations, neurological manifestations, and peripheral circulatory diseases, which served as dependent variables. In this section, the researcher discusses how these complications are associated with different risk factors (e.g. race, gender, obesity, etc.), which were used as independent variables. Obtained data is supported with, and compared to, other empirical studies that have been conducted on this topic. Based on the research gaps, some recommendations for future studies are outlined.

5.1.1 Ketoacidosis

The present study has revealed that ketoacidosis is strongly associated with a variety of risk factors, most significant of which is alcohol abuse (OR=3.303). There are several empirical studies supporting this finding, which demonstrate that alcohol consumption is a significant risk factor for the development of diabetic ketoacidosis [145, 146]. Research indicates that excessive alcohol consumption leads to a series of negative processes in the human body, such as malnutrition and dehydration, which, together with adverse effects of ethanol, lead to the development and onset of T2DM and such related complications as ketoacidosis. As noted in the literature review, evidence exists that quite often, ketoacidosis occurs in patients having no history of alcohol abuse [146]. This

inconsistency in findings may be due to different sample size and populations involved in the cited studies. Nevertheless, discrepancy in findings points to the need to further study the risk factors contributing to the development of this condition, as well as explore what other risk factors may cause diabetic ketoacidosis.

Furthermore, the present study revealed that ketoacidosis is strongly associated with hyperglyceridemia (OR=2.992). Naturally, such a strong connection is supported by many empirical studies, which have been analyzed in the literature review [165, 166, 167, 168]. Notably, these studies found a significant connection between hyperglyceridemia, ketoacidosis, and acute pancreatic. More specifically, it has been found that hypertriglyceridemia-induced pancreatitis may lead to the development of ketoacidosis [167], which highlights the need to explore the adverse effects of hyperglyceridemia and pancreatitis on diabetic patients. Overall, as seen from the literature review, the connection between hyperglyceridemia and ketoacidosis is well established and true for different population groups.

The study has also shown the significant connection between the family history of diabetes and ketoacidosis (OR=1.661). One of the studies that support this project's findings was conducted by Marigliano et al., who found that HLA-associated high-risk genotypes increase the risk of having diabetic ketoacidosis [128]. However, analysis of literature has demonstrated that the data on the association between ketoacidosis and family history is mostly limited to type 1 diabetes, while research on type 2 diabetes is scarce. This gap in literature may suggest that there simply is no connection between genetic factors and ketoacidosis, but the high odds ratio found in this study points that researchers should pay more attention to this under-researched connection. Furthermore, there seems

to be a relationship between ketoacidosis and hypertension (OR=1.549). However, as with the family history as a risk factor for ketoacidosis, hypertension is also studied most often in relation to type 1 diabetes, while cases of type 2 diabetes remain under-researcher. Thus, for example, a study found the connection between blood pressure, dehydration, and ketoacidosis in pediatric patients [155]. However, because this study had different population sample, its results can hardly be supportive of this study's findings.

The present study also found a relationship between ketoacidosis and such risk factors as gender (OR=1.233), race (OR=1.111-1.236 depending on race; Asian or Pacific Islanders and Native Americans were not significant in the model), and smoking (OR=1.149). As previously noted, this connection is also supported in several more studies [26, 105, 106, 107], which allows concluding that the relation is true across different populations. In the present study, statistically significant connection was also found between ketoacidosis and obesity, hyperlipidemia, hypercholesterolemia, asthma, vitamin D deficiency, and age. However, the odds ratio was less than one, which indicates that these risk factors rarely affect the development of ketoacidosis. One needs to note that although such risk factors as low socio-economic status, family problems, and omission of insulin were not studied in the present paper, they were identified as significant predictors of ketoacidosis development [190]. One may suggest, therefore, that ketoacidosis should be studied in connection with many other factors that have not been included in the present research.

5.1.2 Hyperosmolarity

Hyperosmolarity was another independent variable that was studied in its association with diverse risk factors. The most significant statistical association was found

between hyperosmolarity and race. In particular, it has been found that African Americans (OR=2.301) have higher risks of developing this diabetes-related complication than representatives of other races (OR=1.348 for Asian or Pacific Islanders, OR=1.225 for Hispanics, OR=1.358 for other races). Notably, the association between being Native American and developing hyperosmolarity was found statistically insignificant. Unfortunately, despite the severity of this condition, few empirical studies have been found that investigated race as a risk factor for hyperosmolarity. According to a study analysed in literature review, Blacks, Native Americans and Asians are at high risk of hyperosmolarity syndrome [26, 112]. Similarly, African Americans were found to have the increased risk of HHS [113]. These results, however, have been debated in another study. Researchers doubted whether hyperosmolarity occurs more often in African-American patients and suggested that there are no significant racial differences in susceptibility to this complication [114]. As it has been previously noted, this study was conducted 34 years ago and included a small sample size, so its results cannot be considered reliable. Overall, it is logical to suggest that longitudinal, large-scale empirical studies are strongly required to determine the connection between race and hyperosmolarity, as it could help diagnosing diabetes more accurately in different racial groups.

Hyperosmolarity was also found to be associated with hyperglyceridemia (OR=2.193), which has been supported in another empirical study. More specifically, researchers revealed that hypertriglyceridemia and hyperosmolar hyperglycemic syndrome (HHS) are closely related [170]. However, despite the significant odds ratio that has been identified in the present paper, the study by Gosmanov et al. is by far the only credible research that could support this finding [170]. Therefore, more empirical research is

recommended to establish the connection between hyperosmolarity and hyperglyceridemia. Furthermore, the present study has found significant positive correlation between hyperosmolarity and increased alcohol intake (OR=2.006). Similarly, alcohol intake was found to be one of precipitating factors in the hyperosmolar hyperglycemic state [151], which means that alcohol consumption may be viewed as a risk factor in the development of hyperosmolarity. One needs to note, however, that this study is descriptive and does not provide any credible statistics or empirical data. Clearly, hyperosmolarity needs to be studied further concerning its connection with alcohol intake.

Results demonstrated that family history of diabetes is also a statistically significant risk factor for developing hyperosmolarity (OR=1.592). These results have been supported in several credible empirical studies [128, 134, 135]. It is important to note, however, that one of these studies focused on pediatric patients, so its results cannot be compared to the present study. In any case, the connection between genetic factors and hyperosmolarity is well established and can be used in practice to diagnose diabetes in different population groups. Furthermore, statistical analysis has demonstrated that the development of hyperosmolarity in T2DM patients is also associated with hypertension (OR=1.539). Empirical research to support this finding, however, remains scarce. This gap in literature highlights the urgent need to investigate the connection between hypertension and hyperosmolar hyperglycemic syndrome, as it could help practitioners prevent HHS in patients with high blood pressure.

Meanwhile, smoking was found to be another risk factor contributing to the development of hyperosmolarity (OR=1.124). As previously noted, there seems to be no reliable data that could confirm these findings. At the same time, the connection was found

between HHS and underlying infections, medication intake, substance abuse, undiagnosed diabetes, non-compliance, and coexisting disease [151], as well as age 33–44 (vs. >55), African American race (AHR, 2.71, 95 %CI, 1.96–3.75), recipients of cadaver kidneys, and patients with maintenance TAC [109]. This means that possibly, more attention should be paid to other risk factors without focusing specifically on smoking.

Finally, research showed that female gender can also be considered the significant risk factor for hyperosmolarity (OR=1.062). Review of literature, however, has provided inconclusive evidence to support this finding. On the one hand, a population-based study of diabetic patients aged ≥18 years found that women are twice as likely to have hyperosmolarity as men are [108]. On the other hand, it has been found that female gender as a risk factor was non-significant for hyperglycemic hyperosmolar syndrome [109]. This discrepancy in findings may be due to different sample size and population, so further studies are required to address this problem. Obesity, hyperlipidemia, hypercholesterolemia, asthma, vitamin D deficiency, and age 50 and older have also been identified as statistically significant risk factors for hyperosmolarity development, but the odds ratio was less than one. Age 24-49 was found to be statistically insignificant predictor of hyperosmolarity, which was supported in one empirical study [98]. Some of these results (obesity and hypercholesterolemia) have been confirmed in previous empirical studies [112, 113, 118], although obesity as risk factor should be studied in more detail because the existing research focuses disproportionately on pediatric patients.

5.1.3 Renal Manifestations

In the present paper, age was found to be the strongest risk factor for diabetes-related renal complications (OR=3.586 for 65 and older; OR=2.724 for 50-64; OR=2.101

for 35-49; and OR=1.951 for 25-34). Multiple studies have been conducted, which established that the older T2DM patient is, the more predisposed he or she gets to having various renal complications [89, 99, 100, 101]. Thus, empirical data supports the findings provided in the present study, as it vividly demonstrates that the risk of developing diabetes-related renal complication is increasing with age. Furthermore, race has proven to be another important risk factor contributing to renal complications in T2DM patients (OR=3.159 for Asian or Pacific Islanders; OR=1.924 for Hispanics; OR=1.439 for African Americans, OR=1.393 for other races). Several studies discussed in literature review support these findings [116, 117, 118, 119]. In this way, one may suggest that the relationship between race and renal complications is true across many different population groups.

Unlike ketoacidosis and hyperosmolarity, renal complications have proven to be linked to vitamin D deficiency (OR=1.372), which has been supported in credible empirical studies [183, 185]. One needs to note that empirical research provides evidence of a universally true relationship between Vitamin D deficiency and diabetes-associated renal complications. Furthermore, hyperlipidemia was found to be a statistically significant risk factor for renal complications (OR=1.177), with many empirical studies supporting this finding [89, 187]. Thus, the connection between hyperlipidemia and renal manifestations established in this paper can be considered credible. Hypercholesterolemia was also found to be associated with renal complications (OR=1.057), which goes in line with the data provided in reviewed literature [161, 162, 163].

Obesity was another identified risk factor strongly related to renal complications (OR=1.049). This finding is true across many different population groups, which is

demonstrated in several studies [139, 140, 141]. Finally, age, gender, smoking, alcohol abuse, hypertension, and hyperglyceridemia were also found to be statistically significant risk factors for renal complications, but this relation was weaker than in previously identified cases. Notably, reviewed literature supported these findings [89, 132, 144, 150, 171]. Family history of diabetes and asthma were found to be statistically insignificant in the model. Contrary to these findings, however, heritability was found to play an important role in developing diabetic nephropathy [127].

5.1.4 Ophthalmic Manifestations

Ophthalmic manifestations are widespread complications of T2DM, with many risk factors contributing to their development. In the present study, race was found to be the most significant risk factor for diabetes-related ophthalmic diseases (OR=1.431 for Native Americans; OR=1.373 for Hispanics; OR=1.313 for Asians and Pacific Islanders; OR=1.300 for African Americans, and OR=1.290 for other racial groups). These results have been confirmed in list of empirical studies [120, 121, 122], with only one study contradicting the findings [123], which found that race was not associated with diabetic retinopathy in a multi-ethnic Asian population comprised of Chinese, Malays, and Indians. The disparity of results may be explained by the fact that different racial groups were involved.

Furthermore, hyperlipidemia was found to be strongly associated with T2DM ophthalmic manifestations (OR=1.239). Analysis of literature has vividly provided evidence of universally true relationship between the variables. Thus, conducted research identified that in many cases, patients presented with such ophthalmic manifestations as diabetic retinopathy also have high levels of serum total cholesterol [91, 188, 189]. This

169

finding has an important implication for medical practice, as it can potentially help diagnose and treat diabetes-related complications more timely and effectively. Furthermore, hypercholesterolemia (OR=1.199), family history of diabetes (OR=1.140), and hypertension (OR=1.127) were found to be strongly associated with T2DM ophthalmic complications. Analysis of empirical literature allows suggesting that these findings are reliable, as many large-scale, empirical studies have come to the same conclusion [90]. Thus, the reviewed studies showed that high total cholesterol levels increase the risks that a person with T2DM will eventually develop diabetic retinopathy [90]. Furthermore, the risk of having retinopathy is four-fold higher in individuals with familial history of diabetes, which has been found in one of the reviewed studies [126]. Similarly, the connection between hypertension and ophthalmic manifestations has also been supported, as several studies have found statistically significant connection between the two variables [99, 138]. In this way, one may note that this paper's results are in line with the recent empirical data.

Obesity, smoking, alcohol abuse, hyperglyceridemia, and asthma were identified in the present study as statistically significant risk factors for ophthalmic complications, although far less significant than risk factors cited above. Thus, for example, obesity was found to be associated with the onset and progression of diabetic retinopathy, with significant relationship between the variables [90]. The association of smoking, alcohol abuse, hyperglyceridemia, and diabetic retinopathy, however, has been inconsistent in the literature, possibly because of the disparities in sample size and population [172].

Age was found to be statistically insignificant in the present study, which contradicts the existing literature. As identified in review, the relationship between age and

retinopathy in patients <70 is not significant, but the same relationship in patients above 70 years is statistically significant [90]. Similarly, another research found a significant relationship between older age (>65 years) and diabetic retinopathy. These findings can be considered credible because the study was based on an adequate sample size and was sufficiently powered to detect all differences between the variables [91]. The discrepancy of findings between the present research and existing empirical literature is odd, taking into account the high odds ratio found in the studies. Possibly, this may be due to the small sample of people older than 60, so it is preferable to conduct more large-scale empirical studies to establish the relationship between age and T2DM-related ophthalmic complications. Finally, Vitamin D deficiency was not significantly associated with dependent and excluded from the model. This also contradicts the existing research, as one of the reviewed studies found that Vitamin D deficiency is closely associated with the development and progression of diabetic retinopathy in T2DM patients [177].

5.1.5 Neurological Manifestations

Another type of complications that has been explored in the present study is related to neurological manifestations. Thus, it has been found that hypertension is the most significant risk factor for T2DM-related neurological manifestations (OR=3.800), which has been supported in the studies [156, 157, 158, 159]. However, one of the reviewed papers did not find any significant relationship between hypertension and diabetic neuropathy. This discrepancy in findings could be attributed to the small sample size (n=110), which was not enough to adequately detect and analyze all the differences between the study groups. Therefore, longitudinal studies are necessary to confirm the findings of this cross-sectional study. Overall, the majority of studies have been unanimous

171

as to the close connection between hypertension and neurological complications, so one can suggest that the relationship between variables is true across different populations and cases.

Age is another risk factor strongly associated with neurological complications (OR=1.682 for 35-49; OR=1.486 for 25-34, and OR=1.473 for 50-64 age groups). Notably, age 65 and older was found to be statistically insignificant in the model. The majority of the reviewed studies supported these findings, emphasizing the significant relationship between the two variables [87, 102, 103]. One of the studies, however, contradicted this data, as researchers found no connection between the development of diabetic foot and age. On the contrary, empirical data provided by the authors showed that diabetic foot risk decreased with the age [104]. Nevertheless, as previously stressed, the cross-sectional design of this study does not allow establishing a true causal association between age and diabetic foot. In any case, further studies are needed to investigate in more detail the possible impact of age on diabetic-related neurological complications.

Unlike other complications explored in the study, neurological manifestations are strongly related to asthma (OR=1.256). However, there is limited literature that could support this finding, with the majority of studies focusing on the association between lung function and T2DM, without paying specific attention to neurologic complications [184, 185]. More importantly, one of the reviewed studies found no relationship between asthma and development of diabetic neuropathy, which points to the need to confirm the data in future empirical studies [84]. Obesity was also found to be associated with T2DM neurological complications (OR=1.200), with the studies supporting this data [142, 143].

However, research found no connection between obesity and DPN in the Asian population, which allows suggesting that obesity as a risk factor may be related to race [92].

Furthermore, the model showed that gender is associated with neurological complications (OR=1.162). In line with these findings, researchers found that the prevalence of peripheral insensate neuropathy was higher in males (9.7%) than females (7.5%), irrespectively of the diabetic status [192]. Similarly, several other reviewed studies identified a significant relationship between gender and neurological diseases [89, 93, 104, 111]. Smoking was another risk factor related to T2DM neurological complications (OR=1.143), but little empirical evidence exists to support this finding, which highlights the need to study this risk factor in more detail. Thus, only one study found that smoking was a predictor of neurological manifestations, especially stroke [94]. Notably, race, family history of diabetes, hyperlipidemia, hyperglyceridemia, and Vitamin D deficiency were also found to be associated with neurological complications, but the odds ratio in these cases was less than one. Alcohol abuse and hypercholesterolemia were not significantly associated with neurological manifestations, so they were excluded from the model. One needs to note, however, that literature identifies a significant relationship between alcohol consumption and diabetic neuropathy [148, 149], as well as between cholesterol and triglycerides and neuropathy [142]. Clearly, this discrepancy in findings highlights the need of conducting more large-scale studies with adequate dataset.

5.1.6 Peripheral Circulatory Disorders

The last group of complications explored in this study relates to peripheral circulatory disorders. Statistical analysis has demonstrated that age is the most significant risk factor for this variable (OR=22.081 for 65 and older; OR=18.560 for 50-64;

OR=13.648 for 35-49; and 7.994 for 25-34), with the highest odds ratio among all risk factors and complications included in the model. This significant connection is supported in multiple empirical studies on peripheral arterial disease [96, 97], which emphasizes a universally true relationship across all populations and groups. Race was another risk factor identified as a predictor of various peripheral circulatory disorders (OR=1.749 for Hispanic, OR=1.463 for Black, and OR=1.350 for other racial groups). Asian or Pacific Islanders and Native Americans were insignificant in the model. This somewhat contradicts the results provided in the literature, which show that race was significantly associated with PVD in any ethnic groups (Native American-12.0%, Black-8.6%, White-7.4%, Hispanic-4.4%, Asian-4.3%, other-7.4%, P<0.0001) [125]. One can suggest that a larger sample size should be selected in future studies to understand the roots of this discrepancy.

Hypertension was found to be linked with diabetes-associated peripheral circulatory disorders (OR=1.469), with several credible studies supporting this finding in different population groups [69, 153, 154]. In addition, a strong connection was found between this variable and smoking (OR=1.125). This relationship is also confirmed in credible empirical studies [173, 174, 175]. Low (P < 1) but statistically significant connection was found between peripheral circulatory disorders and female gender, obesity, alcohol abuse, hyperlipidemia, hypercholesterolemia, hyperglyceridemia, asthma, and Vitamin D deficiency. While some of these connections, such as obesity, have been supported in the literature, others, such as female gender or asthma have not been proven yet, which means that this gap in literature should be addressed in future studies. Finally,

family history of diabetes was not significantly associated with dependent and so excluded from the model.

5.2. Classification Models

Most of the methods used for classification needs a lot of data in order to get the samples for training, testing and validation. Both, regression and NN classifier, used 6 Diabetes Complications (Ketoacidosis, Hyperosmolarity, Renal, Ophthalmic, Neurological and Peripheral Circulatory Disorders) as a dependent variable, where the independent variables used were Gender (male, female), Race (white, Black, Hispanic, Asian or Pacific Islander, Native American and other), family history of diabetes, obesity, smoking, alcohol related disorders, dyslipidemia, Hypertension, Hypercholesterolemia, Asthma, Vitamin D deficiency and age.

Table 31 contains all the summary regarding the percentage of correct predictions for both model under all the complications. From the table it was visible that ANN and logistic have the same percentage of correct predictions for the complications ketoacidosis, Hyperosmolarity, Ophthalmic Manifestations and Peripheral Circulatory Disorders. Whereas for complication Neurological Manifestations ANN have higher percentage of correct predictions as compare to the Logistic regression and for complication Renal Manifestations Logistic have higher percentage of correct predictions.

Overall table 31 put these both models on the same place. As both models were same for 4 complications and ANN was better in one while logistic was better in other. So to decide that which model was superior to other ROC Curve, misclassification rate. Sensitivity and specificity analysis was used. The figure 46 to 51 contains the ROC curve plotted for each complication under both models i.e. ANN and logistic. According to ROC curve the more

the area a model had under the curve the better it is. From all these six figures we can see that both of these models were approximately covering the same area under the curve except the complication hyperosmolarity. In hyperosmolarity logistic is better than ANN.

Table 31: Classification table summary for diabetes complications

		Observed Group	Predicted Group No	Yes	Percentage Correct
Diabetes Type II with ketoacidosis	Logistic Model	No	392417	28	100.0
		Yes	11620	26	.2
		Overall	404037	54	97.1
	ANN Model	No	392444	1	100.0
		Yes	11646	0	.0
		Overall	404090	1	97.1
Diabetes Type II with Hyperosmolarity	Logistic Model	No	398191	0	100.0
		Yes	5900	0	.0
		Overall	404091	0	98.5
	ANN Model	No	398191	0	100.0
		Yes	5900	0	0.0
		Overall	404091	0	98.5
Diabetes Type II with Renal Manifestations	Logistic Model	No	245556	24059	91.1
		Yes	102993	31483	23.4
		Overall	348549	55542	68.6
	ANN Model	No	249021	20594	92.40
		Yes	107221	27255	20.30
		Overall	356242	47849	68.4
Diabetes Type II with Ophthalmic Manifestations	Logistic Model	No	378559	0	100.0
		Yes	25532	0	.0
		Overall	404091	0	93.7
	ANN Model	No	378559	0	100.0
		Yes	25532	0	0.0
		Overall	404091	0	93.7
Diabetes Type II with Neurological Manifestations	Logistic Model	No	164511	41029	80.0
		Yes	103094	95457	48.1
		Overall	267605	136486	64.3
	ANN Model	No	159219	46321	77.4
		Yes	98108	100443	50.5
		Overall	257327	146764	64.4
Diabetes Type II with Peripheral Circulatory Disorders	Logistic Model	No	376105	0	100.0
		Yes	27986	0	.0
		Overall	404091	0	93.1
	ANN Model	No	376105	8	100.0
		Yes	27969	0	0.0
		Overall	404074	8	93.1

Figure 46: ROC curve for ketoacidosis under both models
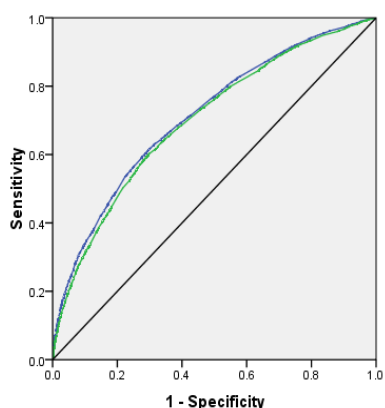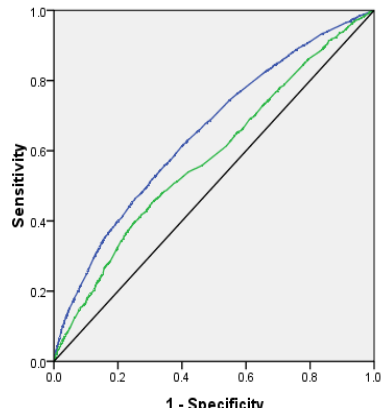

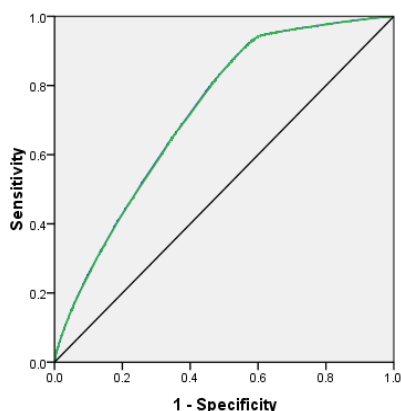**Figure 47: ROC curve for hyperosmolarity under both models**

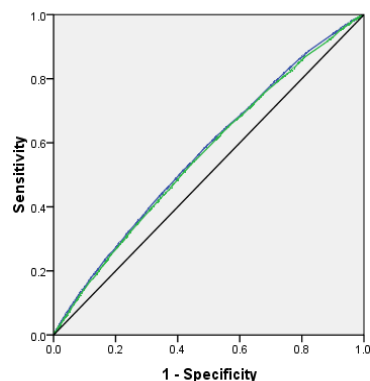**Figure 48: ROC curve for renal manifestation under both models**

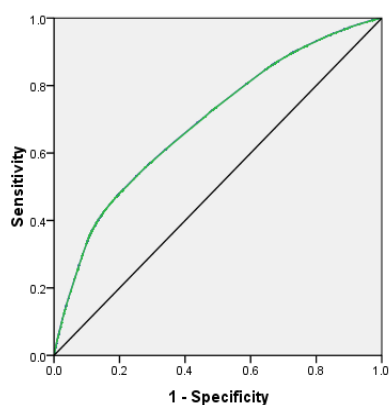**Figure 49: ROC curve for ophthalmic manifestation under both models**

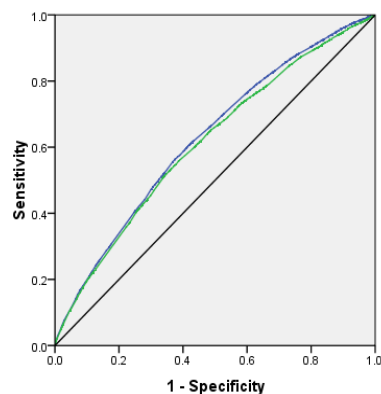**Figure 50: ROC curve for neurological manifestation under both models**

Figure 51: ROC curve for peripheral circulatory disorders under both models

Table 32 contains the Models accuracy rate, Misclassification Rate, Sensitivity and Specificity for both models and all the complications. The formulas and concept of models accuracy rate, misclassification rate, sensitivity and specificity were given in chapter 3.

Table 32: Confusion matrix analysis for diabetes complications

Complications		Logistic Model	Multilayer perceptron
Ketoacidosis	Model Accuracy	0.971175	0.971277
	Misclassification Rate	0.028825	0.028723
	Sensitivity	0.002233	0
	Specificity	0.999929	0.999997
Hyperosmolarity	Model Accuracy	0.985399	0.985399
	Misclassification Rate	0.014601	0.014601
	Sensitivity	0	0
	Specificity	1	1
Renal Manifestations	Model Accuracy	0.685586	0.683697
	Misclassification Rate	0.314414	0.316303
	Sensitivity	0.234116	0.202676
	Specificity	0.910765	0.923617
Ophthalmic Manifestations	Model Accuracy	0.936816	0.936816
	Misclassification Rate	0.063184	0.063184
	Sensitivity	0	0
	Specificity	1	1
Neurological Manifestations	Model Accuracy	0.642583	0.64334
	Misclassification Rate	0.357417	0.35666
	Sensitivity	0.50588	0.480768
	Specificity	0.774638	0.800384
Peripheral Circulatory Disorders	Model Accuracy	0.930743	0.930764
	Misclassification Rate	0.069257	0.069236
	Sensitivity	0	0
	Specificity	1	0.999979

In the table 32 sensitivity for both of the models was 0 most of the time, this was because the predicted column of yes in confusion matrix was zero or almost zero. Bar charts are created in order to see that which complication have higher % of correct predictions and decreased misclassification. These bar charts created from the table 32. In figure 52 the model accuracy rate was compared for logistic regression and multilayer perceptron (ANN), in order to see that which complication model have the highest model accuracy rate. From the Figure 52 it can be seen that Hyperosmolarity have the highest model

accuracy rate following by ketoacidosis and Peripheral Circulatory Disorders. The classification models have the lowest model accuracy rate for the complication neurological manifestations.
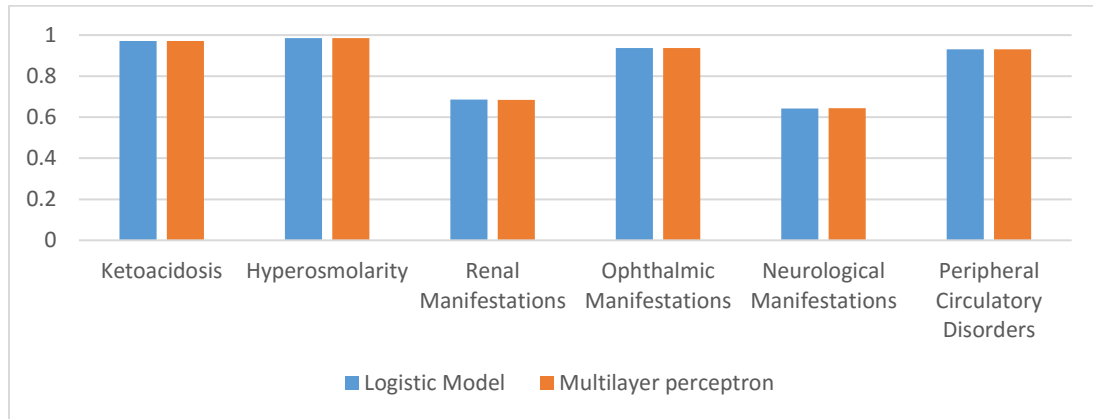
Figure 52: Model accuracy rate for each complication

Similarly, in figure 53 the model misclassification rate is compared for logistic regression and multilayer perceptron (ANN), in order to see that for which complication had the lowest misclassification rate. From the Figure 53 it can be seen that neurological manifestations have the highest model misclassification rate following by renal manifestations and Peripheral Circulatory Disorders. The classification models have the lowest model misclassification rate for the complication Hyperosmolarity.
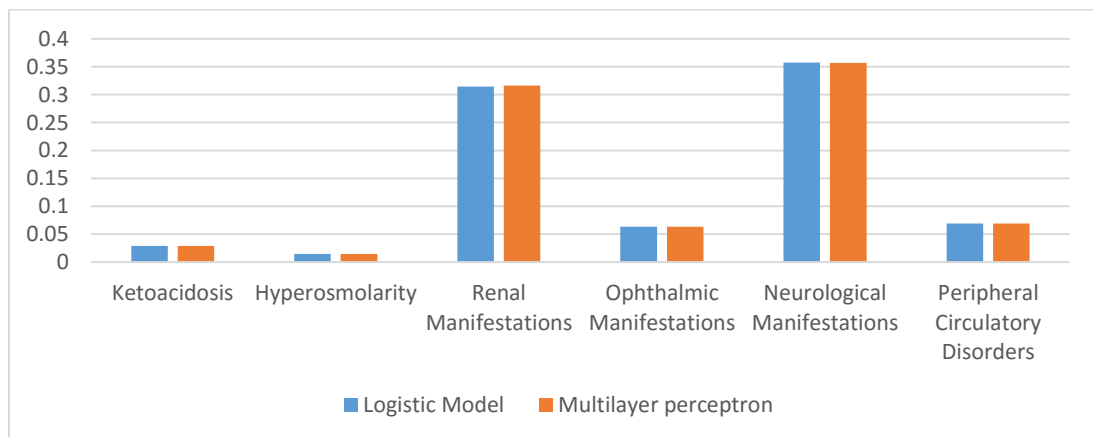
Figure 53: Misclassification rate for each complication

In figure 54 the model sensitivity rate was compared and it can be seen that neurological manifestations had the highest model sensitivity rate following by renal manifestations. Whereas for the rest of the complications models have ignorable sensitivity rates.
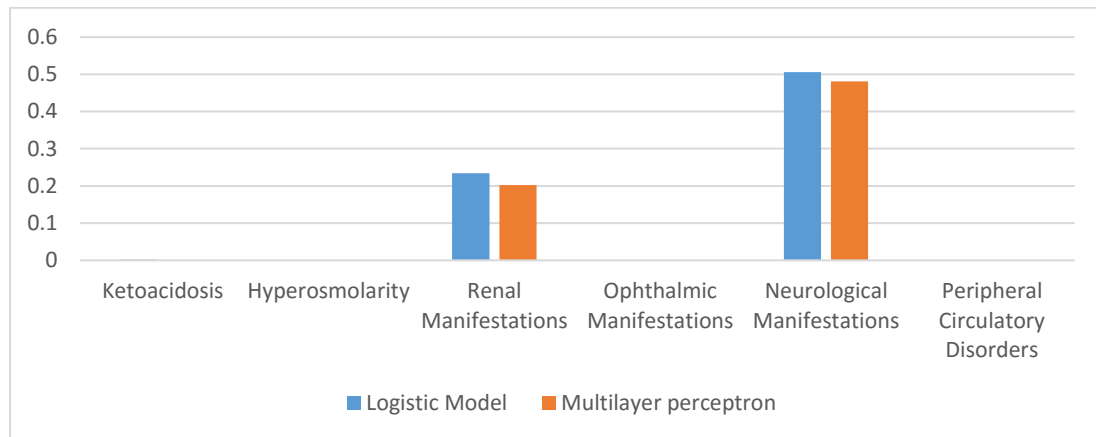
Figure 54: Sensitivity for each complication

In figure 55 the model specificity rate was compared and it was visible that complication Ketoacidosis, Hyperosmolarity, Ophthalmic Manifestations and Peripheral Circulatory Disorders have approximately 100% specificity rate. Neurological Manifestations had the lowest specificity rate.
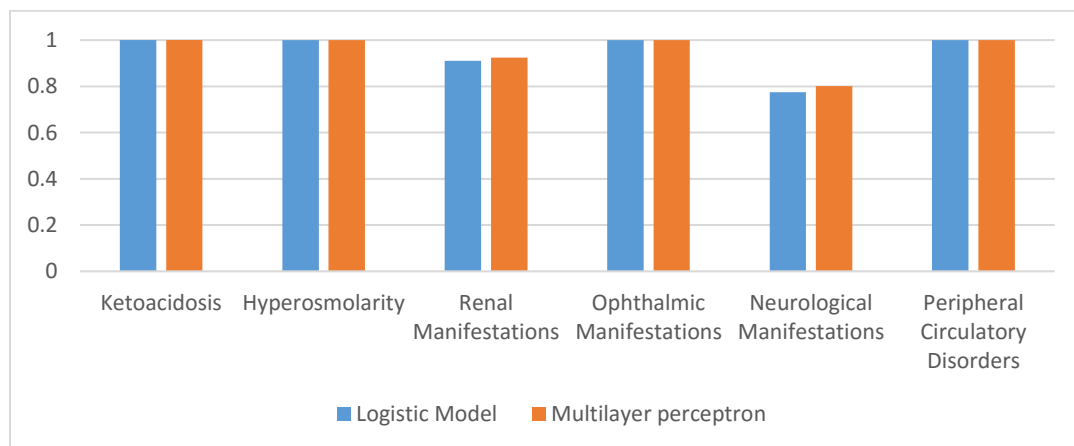
Figure 55: Specificity for each complication

Based on all these comparisons it appears that performance of these both models was same. But these models were not as good as they are supposed to be and their might be a lot of

reasons behind this. The very first and logical reason was the observation were not evenly distributed across the categories of the dependent variables. As we can see from the table 4.7 from Chapter 4 there were only 6.3% patients that have diabetes type-II with Ophthalmic and the rest 93.7% did not have the disease. Similarly, if we look out the confusion matrix given in table 5.1 for the same dependent variable that was Ophthalmic, a whole yes (6.3% of misclassification rate) category was misclassified which means in 100% of data there were only 6% of yes for that dependent variable, and this is way the model prediction rate was high even when a whole category was not correctly classified. These are same situations happening with all the other complications and with multilayer perceptron (ANN).

According to previous studies ANN model is supposed to perform better than logistic model because of the fact that it is one of the most recent and advance classification techniques. Further the way ANN works, it makes ANN more flexible for any kind of data. But again in previous studies comparison between ANN and logistic model is not done for this considerably large sample, because than it might be right to say that performance of these both models is same when sample is relatively large.

CHAPTER VI

VI. SUMMARY AND CONCLUSIONS

6.1 Summary and Conclusions

The present study aimed to find the connection between such T2DM complications as ketoacidosis, hyperosmolarity, renal manifestations, ophthalmic manifestations, neurological manifestations, and peripheral circulatory diseases and most widespread risk factors, such as gender, race, family history of diabetes, obesity, smoking, alcohol-related disorders, hyperlipidemia, hypertension, hypercholesterolemia, asthma, Vitamin D deficiency, and age. While some of the connections have been found as strong and significant, others have not been proven. Thus, for example, the strongest association was found between age and T2DM peripheral circulatory disorders (OR=22.081 for 65 and older; OR=18.560 for 50-64; OR=13.648 for 35-49; and 7.994 for 25-34), with statistics showing that the risk of developing these complications is increasing with age. The strong connection was also found between such risk factors as race (Asian and Pacific Islanders) and age >65 and renal complications, as well as between alcohol abuse and hyperglyceridemia and ketoacidosis (OR=3.303 and 2.992 respectively). furthermore, this study also tried to examine which one of the productive models (Logistic and ANN) is performing better than other under the diabetes type II with complications.

For diabetes type II complication ketoacidosis the model accuracy was 97.1% for both models, while area under the curve was 0.71 for logistic and 0.70 for ANN. Although

these both models have good amount of specificity that is 1 but logistic model have small amount of sensitivity too that is 0.0022. For diabetes type II complication hyperosmolarity the model accuracy is 98.5% for both models, while area under the curve is 0.65 for logistic and 0.61 for ANN and these both models have 0 sensitivity and 1 specificity for complication hyperosmolarity.

For diabetes type II complication renal manifestations the model accuracy is around 68.5% for both models, while area under the curve is 0.72 for logistic and 0.70 for ANN. For logistic sensitivity of the model is 0.23 and specificity of the model is 0.91 whereas for ANN sensitivity and specificity of the model is 0.20 and 0.92 respectively. These both models have some considerable amount of sensitivity and good amount of specificity for the complication renal manifestations.

For diabetes type II complication Ophthalmic Manifestations the model accuracy and area under the curve is 93.7% and 0.65 for both models, while these both models have 0 sensitivity and 1 specificity.

For diabetes type II complication Neurological manifestations the model accuracy is around 64.3% for logistic and 64.4% for ANN, while area under the curve is 0.68 for logistic and 0.70 for ANN. For logistic, sensitivity of the model is 0.35 and specificity of the model is 0.50 whereas for ANN sensitivity and specificity of the model is 0.35 and 0.48 respectively. These both models have some considerable amount of sensitivity and specificity for the complication renal manifestations.

For diabetes type II complication Peripheral Circulatory Disorders the model accuracy is 93.1% for both models, while area under the curve is 0.62 for logistic and 0.60 for ANN. Whereas these both models have 0 sensitivity and 1 specificity.

Over all the best model is the one which have good % of model accuracy and considerable amount of sensitivity and specificity. There are some models with higher % of correct predictions but they do not have good amount of sensitivity and models like this cannot be concluded the best one. Such as logistic and ANN models for complication hyperosmolarity have the highest model accuracy but they have 0 sensitivity. But we cannot say that these both models perform better for hyperosmolarity complication because model does not have sensitivity.

Out of all these complications only three complications turn out to be the best for which the models, logistic and ANN, performs better. These complications are renal manifestations, neurological manifestations and ketoacidosis. Because for these diabetes type II complications both models ANN and logistic performs better than the other three complications. Even for neurological manifestations, ANN model out performs the logistic model due to its higher % of correct predictions and higher area under the curve.

6.2 Further Work

In the end of every study there is always a place for more to consider. So further studies are needed as there are a lot of other factors that may affect the complication development. One of which can be assessing the impact of social parameters and behavioral factors on complication development. Different complication can be used other than the one used in this study. Nevertheless, it is appropriate to establish designing nested case control studies in order to establish association between complication development and proposed risk factors. Using ICD 10 will help to establish better conclusion

REFERENCES

1. American Diabetes Association. Diagnosis and classification of diabetes mellitus. *Diabetes Care*. 2012; 35(1): 64-71.

2. Ozougwu JC, Obimba KC, Belonwu CD, Unakalamba CB. The pathogenesis and pathophysiology of type 1 and type 2 diabetes mellitus. *J Phy Patho.* 2013; 4(4): 46-57.

3. Prasad S, Sajja R, Naik P, Cucullo L. 2014, 'Diabetes mellitus and blood-brain barrier dysfunction: An overview. *J Pharmacovigilence.* 2014; 2(2):125-150.

4. Ghoshal K, Bhattacharyya M. Adiponectin: Probe of the molecular paradigm associating diabetes and obesity', *W J Diabetes.* 2015; 6(1): 151-166.

5. Sun X, Yu W, Hu C. Genetics of Type 2 Diabetes: Insights into the pathogenesis and its clinical application', *BM Res Int.* 2014; 1-15.

6. Centers for Disease Control and Prevention (CDC). *National Diabetes Statistics Report: Estimates of Diabetes and Its Burden in the United States, 2014*. Atlanta, GA: U.S. Department of Health and Human Services; 2014.

7. Mendenhall E, Norris SA, Shidhaye R, Prabhakaran D. Depression and Type 2 Diabetes in Low and Middle Income Countries: A Systematic Review. *Diabetes Res Clin Pract.* 2014; 103(2): 276–285.

8. American Diabetes Association. Standards of medical care in diabetes-2015. *Diabetes Care,* 2015; 38(1):1-2.

9. Inzucchi SE, Bergenstal RM, Buse JB, et al. Management of Hyperglycemia in Type 2 Diabetes: A Patient-Centered Approach: Position Statement of the American Diabetes Association (ADA) and the European Association for the Study of Diabetes (EASD). *Diabetes Care.* 2012; 35(6):1364-1379.

10. Barkoudha E, Skali H, Uno H, et al. Mortality Rates in Trials of Subjects with Type 2 Diabetes. *J Am Heart Assoc.* 2012; 1: 8-15

11. Van Belle TL, Coppieters KT, Herrath MG. Type 1 diabetes: Etiology, immunology, and therapeutic strategies. *Phy Rev.* 2011; 91: 79–118.

12. Drong AW, Lindgren CM, McCarthy MI.The genetic and epigenetic basis of type 2 diabetes and obesity', *Clin Pharm Ther.* 2012; 92(6): 707-715.

13. Bodicoat DH, O'Donovan G, Dalton AM, et al. The association between neighbourhood greenspace and type 2 diabetes in a large cross-sectional study. *BMJ Open.* 2014; 4(12): e006076.

14. Cheema A, Adeloye D, Sidhu S, Sridhar D, Chan KY. Urbanization and prevalence of type 2 diabetes in Southern Asia: A systematic analysis. *J Glob Health.* 2014; 4(1): 010404.

15. Simmons RK, Rahman M, Jakes RW et al. Effect of population screening for type 2 diabetes on mortality: long-term follow-up of the Ely cohort. *Diabetologia.* 2011; 54: 312–319.

16. Ekoe J-M, Punthakee Z, Ransom T, et al. Screening for Type 1 and Type 2 Diabetes: Canadian Diabetes Association Clinical Practice Guidelines Expert Committee. *Can J Diabetes.* 2013; 37: S12-S15.

17. Group Health. *Type 2 diabetes: Screening and treatment guideline.* Group Health Cooperative. 2013;1-20.

18. Rutten G. Screening for type 2 diabetes—where are we now? *The Lancet.* 2010; 1-3.

19. Zhao C, Wang W, Ding W, et al. Insulin and risk of diabetic retinopathy in patients with type 2 diabetes mellitus: Data from a meta-analysis of seven cohort studies. *Diagnostic Pathology.* 2014, 9:130.

20. Alonso-Moran E, Orueta JF, Fraile JS, et al. The prevalence of diabetes-related complications and multimorbidity in the population with type 2 diabetes mellitus in the Basque Country. *BMC Public Health*. 2014; 14:1059.

21. Toro R, Segura E, Millan J, et al. Relationship between lipoprotein (a) and micro/macro complications in type 2 diabetes mellitus: A forgotten target. *J Geriatric Cardiology.* 2015; 12: 93−99.

22. Low JC, Felnera EI, Muir AB et al. Do obese children with diabetic ketoacidosis have type 1 or type 2 diabetes? *Prim Care Diabetes.* 2012; 6(1):61–65.

23. Smiley D, Chandra P, Umpierrez GE. Update on diagnosis, pathogenesis and management of ketosisprone Type 2 diabetes mellitus. *Diabetes Manag (Lond).* 2011; 1(6): 589–600.

24. Westerberg DP. Diabetic Ketoacidosis: Evaluation and Treatment. *Am Fam Physician.* 2013;87(5):337-346.

25. Lin MV, Biship G, Benito-Herrero H, Diabetic Ketoacidosis in Type 2 Diabetics: A Novel Presentation of Pancreatic Adenocarcinoma. *J Gen Intern Med*. 2009; 25(4):369–73.

26. Dabelea D, Rewers A, Stafford JM et al. Trends in the prevalence of ketoacidosis at diabetes diagnosis: The SEARCH for diabetes in youth study. *Pediatrics.* 2014; 133(4):938-945.

27. McFarlane P, Gilbert RE, MacCallum L. Chronic Kidney Disease in Diabetes: Canadian Diabetes Association Clinical Practice Guidelines Expert Committee. *Can J Diabetes.* 2013; 37: S129-S136.

28. Longo-Mbenza B, Muaka MM. The Protective Effect of Phaseolus Vulgaris on Cataract in Type 2 Diabetes: A Profitable Hypothesis Med Hypothesis. *Discov Innov Ophthalmol.* 2013; 2(4): 105–108.

29. Bello NA, Pfeffer MA, Skali H, et al. Retinopathy and clinical outcomes in patients with type 2 diabetes mellitus, chronic kidney disease, and anemia. *BMJ Open Diabetes Res Care*. 2014;2:e000011.

30. Boyd SR, Advani A, Altomare F, Stockl F. Retinopathy: Clinical Practice Guidelines. *Can J Diabetes.* 2013; 37: S137eS141.

31. Dedov I, Maslova O, Suntsov Y, et al. Prevalence of Diabetic Retinopathy and Cataract in Adult Patients With Type 1 And Type 2 Diabetes in Russia. *Rev Diabet Stud.* 2009; 6(2): 124–129.

32. Fowler MJ. Microvascular and Macrovascular Complications of Diabetes. *Clinical Diabetes.* 2008; 26(2): 77-82.

33. Li L, Wan X, Zhao G. Meta-analysis of the risk of cataract in type 2 diabetes. *BMC Ophthalmol.* 2014; 14: 94. doi: [10.1186/1471-2415-14-94](10.1186/1471-2415-14-94).

34. Stoner GD. Hyperosmolar Hyperglycemic State. *Am Fam Physician.* 2005; 71(9):1723-1730

35. Beckman JA, Paneni F, Casentino F, Creager MA. Diabetes and vascular disease: Pathophysiology, clinical consequences, and medical therapy: part II. *Eur Heart J.* 2013; 142: 2444-2452.

36. Pradeepa R, Chella S, Surendar J, et al. Prevalence of peripheral vascular disease and its association with carotid intimamedial thickness and arterial stiffness in type 2 diabetes: The Chennai Urban Rural Epidemiology Study (CURES 111). *Diab Vascu Dis Res.* 2014; 11(3) 190–200.

37. Althouse AD, Abbott JD, Suton-Tyrell K, et al. Favorable effects of insulin sensitizers pertinent to peripheral arterial disease in type 2 diabetes: Results from the Bypass Angioplasty Revascularization Investigation 2 Diabetes (BARI 2D) trial. *Diabetes Care.* 2013; 36(10): 3269–3275.

38. Alonso-Moran E, Orueta JF, Esteban JIF, et al. The prevalence of diabetes-related complications and multimorbidity in the population with type 2 diabetes mellitus in the Basque Country. *BMC Pub Heal.* 2014; 14:1059.

39. Laakso M. Cardiovascular disease in type 2 diabetes from population to man to mechanisms. *Diab Care.* 2010; 33(2): 442-449.

40. Franks PW. The Complex Interplay of Genetic and Lifestyle Risk Factors in Type 2 Diabetes: An Overview. *Scientifica.* 2012; 1-11. Was 38 initially.

41. Murad MA, Abdulmageed SS, Iftikhar R, et al. Assessment of the common risk factors associated with Type 2 Diabetes Mellitus in Jeddah. *International Journal of Endocrinology*. 2014; 1-9.

42. Skar M, Villumsen AB, Christensen DL, et al. Increased risk of type 2 diabetes with ascending social class in urban South Indians is explained by obesity: The

Chennai urban rural epidemiology study (CURES-116). *Indian J Endocrinol Metab*. 2013; 17(6): 1084–1089.

43. Boada CA, Martínez-Moreno JM. 2013, 'Pathophysiology of diabetes mellitus type 2: beyond the duo "insulin resistance-secretion deficit. *Nutricion Hospitalaria*. 2013; 28(2): 78-87.

44. Suastika K, Dwipayana P, Semadi MS, Kuswardidhani T. Age is an Important Risk Factor for Type 2 Diabetes Mellitus and Cardiovascular Diseases. *Open Science*. 2012; 67-80.

45. Dai DF, Rabinovitch PS, Ungvari Z. Mitochondria and cardiovascular aging. *Circ Res.* 2012; 110:1109-1124.

46. Suastika K, Dwipayana P, Saraswati IMR, Kuswardhani T, Astika N, Putrawan IB, Matsumoto K, Kajiwara N, Taniguchi H. Relationship between age and metabolic disorder in the population of Bali. *J Clin Gerontol Geriatrics.* 2011; 30: 1-6.

47. Nile DL, Brown AE, Kumaheri MA, et al. Age-related mitochondrial DNA depletion and the impact on pancreatic beta cell function. *PLoS One.* 2014; 9(12): e115433.

48. Rao PV. Type 2 diabetes in children: Clinical aspects and risk factors. *Indian J Endocrinol Metab.* 2015; 19(Suppl 1): S47–S50.

49. Steyn NP, Mann J, Bennett PH, et al. Diet, nutrition and the prevention of type 2 diabetes. *Public Health Nutrition.* 2004; 7(1): 147–165.

50. Hussain A, Hydrie MZ, Claussen B, Asghar S. 2010, 'Type 2 Diabetes and obesity: A review', *J Diabetology,* 2010; 2(1):1-7.

51. Day C, Bailey CJ. Obesity in the pathogenesis of type 2 diabetes. *Br J Diabetes Vas Dis.* 2011;11:55-61.

52. Biesenbach G, Bodlaj G, Pieringer H. Gender-associated Differences in Weight Gain, Insulin Requirement and Metabolic Control in Newly Insulin-treated Type 2 Diabetic Patients with Secondary Sulfonylurea Failure—a One-year Observation. *Clinical Medicine: Endocrinology and Diabetes.* 2009; 2: 75–80.

53. Khalangot MD, Gurianov VG, Vaiserman AM. Gender differences in prevalence of diagnosed type 2 diabetes and patient's body mass index in five Ukraine regions with diverse historical backgrounds. *Bio.* 2012; 2: 1-10.

54. Kwon SK. Women Are Diagnosed with Type 2 Diabetes at Higher Body Mass Indices and Older Ages than Men: Korea National Health and Nutrition Examination Survey 2007–2010. *Diabetes Metab J.* 2014; 38:74-80

55. Awa WL, Fach E, Krakow D, et al. Type 2 diabetes from pediatric to geriatric age: analysis of gender and obesity among 120 183 patients from the German/Austrian DPV database. *Eur J Endocrinol.* 2012; 167: 245–254.

56. Chow EA, Foster H, Gonzalez V, McIver L. The Disparate Impact of Diabetes on Racial/Ethnic Minority Populations. *Clinical Diabetes.* 2012; 30(3): 130-133.

57. Lopez JM, Bailey RA, Rupnow MFT, et al. Characterization of Type 2 Diabetes Mellitus Burden by Age and Ethnic Groups Based on a Nationwide Survey. *Clin Ther.* 2014; 36:494–506.

58. Rosenbaum M, Fennoy I, Accacha S, et al. Racial/Ethnic Differences in Clinical and Biochemical Type 2 Diabetes Mellitus Risk Factors in Children. *Obesity.* 2013; 21: 2081–2090.

59. Dalsgaard E-M, Skriver MV, Sandbaek A, Vestergaard M. Socioeconomic position, type 2 diabetes and long-term risk of death. PLoS ONE. 2015;10(5): e0124829.

60. Feng D, Liu T, Wang H, et al. Mediation Role of C-Reactive Protein on the Association between Smoking Quantity and Type 2 Diabetes in Current Chinese Smokers. *J Diabetes Res.* 2014; 1-7.

61. Radzeviciene L, Ostrauskas R. Smoking habits and the risk of type 2 diabetes: A case-control study. *Diabetes Met*. 2009; 35: 192-197.

62. Luo J, Rossouw J, Tong ST, et al. Smoking and Diabetes: Does the Increased Risk Ever Go Away? *Am J Epidemiol.* 2013;178(6):937–945.

63. Wang Y, Ji J, Liu Y-j, Deng X, He Q. Passive Smoking and Risk of Type 2 Diabetes: A Meta-Analysis of Prospective Cohort Studies. *PLoS ONE*. 2013. 8(7): e69915. doi:10.1371/journal.pone.0069915

64. Chang SA. Smoking and Type 2 Diabetes Mellitus. *Diabetes Metab J.* 2012;36:399-403.

65. Li H, Wang G, Wang A, et al. Alcohol consumption and risk of type 2 diabetes in Mongolian population, Inner Mongolia, China. *J Diab Met*. 2011; 2(1): 1-5.

66. Baliunas DO, Taylor BJ, Irving H, et al. Alcohol as a risk factor for type 2 diabetes: A systematic review and meta-analysis. *Diabetes Care.* 2009; 32:2123–2132.

67. Valliyot B, Sreedharan J, Muttappallymyalil J, Valliyot SB. Risk factors of type 2 diabetes mellitus in the rural population of north Kerala, India: A case control study. *Diabetologia Croatica*. 2013; 42(1): 33-40.

68. Xu F, Ware RS, Tse LA, et al. Joint Associations of Physical Activity and Hypertension with the Development of Type 2 Diabetes among Urban Men and Women in Mainland China. *PLoS One.* 2014; 9(2): e88719.

69. Salman M, Dasgupta S, D'Souza CJ, et al. Impact of Hypertension on Type 2 Diabetes in Mysore Population of South India. *Inter J Clin Med.* 2013; 4: 561-570.

70. Vogt A. The genetics of familial hypercholesterolemia and emerging therapies. Appl Clin Gen. 2015:8 27–36.

71. Zanetti M, Zenti M, Barazzoni R, et al. HELP LDL apheresis reduces plasma pentraxin 3 in familial hypercholesterolemia. *PLoS ONE.* 9(7): e101290. doi:10.1371/journal.pone.0101290.

72. Smith DA. The dyslipidemia of type 2 diabetes: Treatment strategies. *Consultant.* 2013;53(3):137-144

73. Huri HZ. Dyslipidemia and type 2 diabetes mellitus: Implications and role of antiplatelet agents in primary prevention of cardiovascular disease, Dyslipidemia-From Prevention to Treatment, Prof. Roya Kelishadi (Ed.), ISBN: 978-953-307-904-2, InTech,

74. Vijayaraghavan K. Treatment of dyslipidemia in patients with type 2 diabetes. *Lipids in Health and Disease.* 2010; 9: 144-155.

75. Yuan G, Al-Shali KZ, Hegele RA, Hypertriglyceridemia: its etiology, effects and treatment. *CMAJ.* 2007; 176(8): 1113-1120.

76. Tenenbaum A, Klempfner R, Fisman E. Hypertriglyceridemia: a too long unfairly neglected major cardiovascular risk factor. *Cardiovas Diabetol.* 2014, 13:159-168.

77. Chagas CEA, Borges MC, Martini LA, et al. Focus on Vitamin D, Inflammation and Type 2 Diabetes. *Nutrients.* 2012; 4: 52-67.

78. Davis SV. Vitamin D Deficiency and Type 2 Diabetes in African Americans: The Common Denominators. *Diabetes Spectrum.* 2011; 24(3): 148-153.

79. Grineva EN, Karonova T, Micheeva E, Belyaeva O, & Nikitina IL. Vitamin D deficiency is a risk factor for obesity and diabetes type 2 in women at late reproductive age. *Aging.* 2012; 5(7): 575-581.

80. Mitri J, Murau MD, Pittas AG. Vitamin D and type 2 diabetes: A systematic review. *Eur. J Clin Nutr*. 2011; 65: 1005–1015.

81. Mueller NT, Koh W-P, Odegaard AO, et al. Asthma and the risk of type 2 diabetes in the Singapore Chinese Health Study. *Diabetes Res Clin Pract.* 2013; 99(2): 192–199.

82. Song Y, Klevak A, Manson JE, Buring JE, Liu S. Asthma, chronic obstructive pulmonary disease, and type 2 diabetes in the Women's Health Study. Diabetes Res Clin Pr. 2010;90(3):365–71.

83. Yun HD, Knoebel E, Fenta Y, Gabriel SE, Leibson CL, Loftus EV, Jr, et al. Asthma and proinflammatory conditions: a population-based retrospective matched cohort study. Mayo Clinic Proc. 2012;87(10):953–60.

84. Rana JS, Mittleman MA, Sheikh J, Hu FB, Manson JE, Colditz GA, et al. Chronic obstructive pulmonary disease, asthma, and risk of type 2 diabetes in women. Diabetes Care. 2004;27(10):2478–84.

85. Bhatnagar S, Dinesh M. The impact of socio-demographic factors on comorbidity burden in diabetes mellitus patients. Newark: Rutgers, The State University of New Jersey; 2015

86. Bamashmous H, Haque S, Srinivasan S, Dinesh M. The predictors of hospital mortality among adult patients with diabetes. Newark: Rutgers, The State University of New Jersey; 2015.

87. Popescu S, Timar B, Baderca F, et al. Age as an independent factor for the development of neuropathy in diabetic patients. ClinInterv Aging. 2016; 11: 313–318.

88. Barski L, Nevzorov R, Rabaev E, Jotkowitz A, Harman-Boehm I, Zetkser M et al. Diabetic Ketoacidosis: Clinical characteristics, precipitating factors and outcomes of care. IMAJ. 2012;14: 299-302.

89. Al-Rubeaan K, Youssef A., Subhani S, Ahmad N, Al-Sharqawi A., Al-Mutlaq. Diabetic Nephropathy and Its Risk Factors in a Society with a Type 2 Diabetes Epidemic: A Saudi National Diabetes Registry-Based Study. PLOS One. 2014.

90. Liu L, Wu J, Yue S, Geng J, Lian J, Teng W, Chen L. Incidence Density and Risk Factors of Diabetic Retinopathy Within Type 2 Diabetes: A Five-Year Cohort Study in China. International Journal of Environmental Research and Public Health.2015: 7899-7909.

91. Zhang H, Wang J, Ying G, Shen L, Zhang Z. Serum lipids and other risk factors for diabetic retinopathy in Chinese type 2 diabetic patients. J Zhejiang Univ-Sci B (Biomed &Biotechnol). 2013; 14(5):392-399.

92. Morkid, K., Ali, L., & Hussain, A. Risk factors and prevalence of diabetic peripheral neuropathy: A study of type 2 diabetic outpatients in Bangladesh. Int J Diabetes Dev Ctries.2010; 30(1):11-7.

93. Booya F, Bandarian F, Larijani B, Pajouhi M, Nooraei M, Lotfi J. Potential risk factors for diabetic neuropathy: a case control study. BMC neurology. 2005 Dec 10;5(1):1.

94. Giorda CB, Avogaro A, Maggini M, et al. Incidence and Risk Factors for Stroke in Type 2 Diabetic Patients: The DAI Study. Stroke. 2007;38:1154-1160.

95. Althouse, A., Abbott, J., Forker, A., Bertolet, M., Mitchell, E., Thurston, R et al. Risk Factors for Incident Peripheral Arterial Disease in Type 2 Diabetes: Results from the Bypass Angioplasty Revascularization Investigation in Type 2 Diabetes (BARI 2D) Trial. Diabetes Care. 2010:37; 1346-1352.

96. Agarwal, A. K., Singh, M., Arya, V., Garga, U., Singh, V. P., & Jain, V. (2012). Prevalence of peripheral arterial disease in type 2 diabetes mellitus and its correlation with coronary artery disease and its risk factors. JAPI, 60, 28-32.

97. Rhee, S. Y., & Kim, Y. S. (2015). Peripheral arterial disease in patients with type 2 diabetes mellitus. Diabetes Metab J., 39(4), 283-290. doi: 10.4093/dmj.2015.39.4.283

98. Franconi, F., Campesi, I., Occhioni, S., &Tonolo, G. Sex-gender differences in diabetes vascular complications and treatment. Endocrinology, Metabolic & Immune Disorders-Drug Targets.2012:12; 179-196.

99. Retnakaran, R., Cull, C. A., Thorne, K. I., Adler, A. I., & Holman, R. R. (2006). Risk factors for renal dysfunction in type 2 diabetes. Diabetes, 55(6), 1832-1839. http://dx.doi.org/10.2337/db05-1620

100. Viswanathan, V., Tilak, P., &Kumpatla, S. (2012). Risk factors associated with the development of overt nephropathy in type 2 diabetes patients: A 12 years observational study. Indian J Med Res., 136(1), 46-53.

101. Alwakeel, J. S., Isnani, A. C., Alsuwaida, A., AlHarbi, A., Shaikh, S. A., AlMohaya, S., & Ghonaima, M. A. (2011). Factors affecting the progression of diabetic nephropathy and its complications: A single-center experience in Saudi Arabia. Ann Saudi Med., 31(3), 236–242. doi: 10.4103/0256-4947.81528

102. Bansal, D., Gudala, K., Muthyala, H., Esam, H. P., Nayakallu, R., &Bhansal, A. (2014). Prevalence and risk factors of development of peripheral diabetic neuropathy in type 2 diabetes mellitus in a tertiary care setting. J Diabetes Invest., 5, 714-721. doi: 10.1111/jdi.12223

103. Mørkrid, K. (2007). The prevalence of and risk factors for diabetic peripheral neuropathy among type 2 diabetic outpatients in Bangladesh (Ph.M. thesis). Retrieved from https://www.duo.uio.no/bitstream/handle/10852/30151/69091.pdf?sequence=1

104. Nehring P, Mrozikiewic-Rakowska B, Krzyzewska M, et al. Diabetic foot risk factors in type 2 diabetes patients: a cross-sectional case control study. J Diabetes & Metabolic Dis. 2014;13:79-83.

105. Bacos K, Gillberg L, Volkov P, et al. Blood-based biomarkers of age-associated epigenetic changes in human islets associate with insulin secretion and diabetes. Nat Commun. 2016; 7: 11089.

106. Barski, L., Harman-Boehm, I., Nevzorov, R., Rabaev, E., Zektser, M., Jotkowitz, A. B., …Almog, Y. (2011). Gender-related differences in clinical characteristics and outcomes in patients with diabetic ketoacidosis. Gend Med., 8(6), 372-7. doi: 10.1016/j.genm.2011.09.032

107. Azzopardi, P., Brown, A. D., Zimmet, P., Fahy, R. E., Dent, G. A., Kelly, M. J., Wren, S. J. (2012). Type 2 diabetes in young Indigenous Australians in rural and remote areas: diagnosis, screening, management and prevention. Med J., 197(1), 32-36. doi: 10.5694/mja12.10036

108. English, P., & Williams, G. (2004). Hyperglycaemic crises and lactic acidosis in diabetes mellitus. Postgrad Med J., 80, 253-261. doi:10.1136/pgmj.2002.004291

109. Abbott, K. C., Bernet, V. J., Agodoa, L. Y., & Yuan, C. M. (2003). Diabetic ketoacidosis and hyperglycemic hyperosmolar syndrome after renal transplantation in the United States. BMC EnmdocrDisord., 3, 1. doi: 10.1186/1472-6823-3-1

110. Chatziralli, I. P., Sergentanis, T., Keryttopoulos, P., Vatkalis, N., Agorastos, A., &Papazisis, L. Risk factors associated with diabetic retinopathy in patients with diabetes mellitus type 2. BMC Research Notes. 2010.

111. Akram J, Aamir A-H, Basit A, et al. (2011). Prevalence of peripheral arterial disease in type 2 diabetics in Pakistan. J Pakistan MedAsso. 2011; 61(7): 644-648.

112. Maggiore, A. Recognizing and treating hypoglycemia, hyperglycemia and other diabetes-related health problems. JEMS. 2013: 38(12).

113. Tsai, S. L., Hadjiyannakis, S., & Nakhla, M. Hyperglycemic hyperosmolar syndrome at the onset of type 2 diabetes mellitus in an adolescent male. Paediatrics & Child Health. 2012: 17(1); 24–26.

114. Knight, G., &Leatherdale, B. I. (1982). The role of race and environment in the development of hyperosmolar hyperglycaemic non-ketotic coma. Postgraduate Medical Journal, 58, 351-353.

115. Liang, Y., Yan, Z., Sun, B., Chai, C., Jiang, H., Song, A et al. Cardiovascular Risk Factor Profiles for Peripheral Artery Disease and Carotid Atherosclerosis among Chinese Older People: A Population-Based Study. PLos One.2014: 9(1).

116. Bhalla V, Zhao B, Kristen M, Wang E, Choi S, Wong E et al. Racial/Ethnic Differences in the Prevalence of Proteinuric and Nonproteinuric Diabetic Kidney Disease. Diabetes Care. 2012: 36(5);1215-1221

117. Retnakaran R, Cull C, Thorne K, Adler A, Holman R. Risk Factors for Renal Dysfunction in Type 2 Diabetes U.K. Prospective Diabetes Study 74. Diabetes. 2006.

118. Young, J. H. M., Tay, M. K., Lau, D. C. Y., &Huen, K. F. (2014). An emerging challenge in paediatric obesity: A 13-year-old boy with life-threatening hyperosmolar hyperglycaemic syndrome. HK J Paediatr (New Series), 19, 89-92.

119. Earle, K. A., Porter, K. K., Ostberg, J., &Yudkin, J. S. (2001). Variation in the progression of diabetic nephropathy according to racial origin. Nephrol. Dial. Transplant., 16(2), 286-290. doi: 10.1093/ndt/16.2.286

120. Harris M, Klein R, Cowie C, Rowland M, Byrd-Holt D. Is the risk of diabetic retinopathy greater in Non-Hispanic Blacks and Mexican Americans than in Non-Hispanic Whites with type 2 diabetes? Diabetes Care. 1998.

121. Chow, E. A., Foster, H., Gonzalez, V., & McIver, L. (2012). The disparate impact of diabetes on racial/ethnic minority populations. Clinical Diabetes, 30(3), 130-133. http://dx.doi.org/10.2337/diaclin.30.3.130

122. Zhang, X., Saaddine, J. B., Chou, C.-F., Cotch, M. F., Cheng, Y. J., Geiss, L. S., & Klein, R. (2010). Prevalence of diabetic retinopathy in the United States, 2005-2008. JAMA, 304(6), 649-656. doi:10.1001/jama.2010.1111

123. Chiang, P. P., Lamoureux, E. L., Cheung, C. Y., Sabanayagam, C., Wong, W., Tai, E. S., … Wong, T. Y. (2011). Racial differences in the prevalence of diabetes but not diabetic retinopathy in a multi-ethnic Asian population. Invest Ophthalmol Vis Sci., 52(10), 7586-92. doi: 10.1167/iovs.11-7698

124. Yadav R, Tiwari P, Dhanaraj E. Risk factors and complications of type 2 diabetes in Asians. CRIPS. 2008; 9(2):8-12.

125. Berger, J. S., Adelman, M. A., Riles, T. S., &Rockman, C. B. (2011). Abstract 13135: Demographics, clinical risk factors and peripheral vascular disease among 3.6 million adults. Circulation, 124, A13135.

126. Kuo JZ, Wong TY, Rotter JI. Challenges in elucidating the genetics of diabetic retinopathy. JAMA Ophthalmol. 2014;132: 96–107.

127. Ma RCW. Genetics of cardiovascular and renal complications in diabetes. J Diabetes Investig. 2016; 7: 139–154.

128. Marigliano, M., Morandi, A., Maschio, M., Costantini, S., Contreas, G., D'Annunzio, G., …Maffeis, C. (2012). Diabetic ketoacidosis at diagnosis: Role of family history and class II HLA genotypes. Eur J Endocrinol., 168(1), 107-11. doi: 10.1530/EJE-12-0541

129. Langefeld CD, Beck SR, Bowden DW, et al. Heritability of GFR and albuminuria in Caucasians with type 2 diabetes mellitus. Am J Kidney Dis. 2004; 43: 796–800.

130. Igo RP Jr, Iyengar SK, Nicholas SB, et al. Genomewide linkage scan for diabetic renal failure and albuminuria: the FIND study. Am J Nephrol. 2011; 33: 381–389.

131. Janssen B, Hohenadel D, Brinkkoetter P, et al. Carnosine as a protective factor in diabetic nephropathy: association with a leucine repeat of the carnosinase gene CNDP1. Diabetes. 2005; 54: 2320–2327.

132. Kullo, I. J., & Leeper, N. J. (2015). The genetic basis of peripheral arterial disease: Current knowledge, challenges, and future directions. Circulation Research, 116, 1551-1560. doi: 10.1161/CIRCRESAHA.116.303518

133. Han, E., Yun, Y., Kim, G., Lee, Y., Wang, H. J., Lee, b.-W., ... Kang, E. S. (2016). Effects of Omega-3 Fatty Acid supplementation on diabetic nephropathy progression in patients with diabetes and hypertriglyceridemia. PLOS one. Retrieved from http://journals.plos.org/plosone/article?id=10.1371/journal.pone.0154683

134. Rosenbloom, A. L. (2010). Hyperglycemic hyperosmolar state: An emerging pediatric problem. The Journal of Pediatrics, 152(2), 180-184. doi: http://dx.doi.org/10.1016/j.jpeds.2009.11.057

135. Kitabchi, A. E., Umpierrez, G. E., Miles, J. M., & Fisher, J. N. (2009). Hyperglycemic crises in adult patients with diabetes. Diabetes Care, 32(7), 1335-1343. doi: 10.2337/dc09-9032

136. Moued, M. M., Al-Agha, A. E., & Ahmad, I. A. (2013). Hyperosmolar hyperglycemic state (HHS) in newly diagnosed child with type 1 diabetes mellitus: A case report. Turk J EndocrinolMetab., 17, 19-21.

137. Masuo K, Rakugi H, Ogihara T, et al. Cardiovascular and renal complications of type 2 diabetes in obesity: role of sympathetic nerve activity and insulin resistance. Curr Diabetes Rev. 2010; 6(2):58-67.

138. Wijesuriya MA, De-Abrew WK, Weerathunga A, Perera A, Vasantharajah L. Association of chronic complications of type 2 diabetes with the biochemical and physical estimations in subjects attending single visit screening for complications. J Diabetology. 2012; 3:1-10.

139. Bayliss, G., Weinrauch, L. A., &D'Elia, J. A. (2012). Pathophysiology of obesity-related renal dysfunction contributes to diabetic nephropathy. CurrDiab Rep., 12(4), 440-6. doi: 10.1007/s11892-012-0288-1

140. Chen, H.-M., Shen, W.-W., Ge, Y.-C., Zhang, Y.-D., Xie, H.-L., & Liu, Z.-H. (2013). The relationship between obesity and diabetic nephropathy in China. BMC Nephrology, 14, 69. doi: 10.1186/1471-2369-14-69

141. Chang, S. A. (2012). Smoking and type 2 diabetes mellitus. Diabetes Metab J., 36(6), 399-403. doi: 10.4093/dmj.2012.36.6.399

142. Al-Khaabi, J., Maskari, F., Zoubeidi, T., Abdulle, A., Shah, S., Cragg, P et al. Peripheral Artery Disease in Type 2 Diabetic Patients from the United Arab Emirates. Journal of Diabetes & Metabolism. 2014.

143. Smith, A. G., & Singleton, J. R. (2013). Obesity and hyperlipidemia are risk factors for early diabetic neuropathy. J Diabetes Complications, 27(5), 436-442. doi: 10.1016/j.jdiacomp.2013.04.003

144. Ahmed, M., Kishore, G., Khader, H., &Kasturirangan, M. Risk factors and management of diabetic nephropathy. Saudi Journal of Kidney Diseases and Transplantation. 2013.1242-1247.

145. Distel, C., Jacobson, S., &Tille, P. M. (2013). Alcohol induced diabetic ketoacidosis exacerbated by an acute respiratory infection with klebsiella pneumoniae. Clinical Laboratory Science, 26(2), 68-71.

146. Hockenhull, J., Dhillo, W., Andrews, R., & Paterson, S. (2012). Investigation of markers to indicate and distinguish death due to alcoholic ketoacidosis, diabetic ketoacidosis and hyperosmolar hyperglycemic state using post-mortem samples. Forensic Science International (Online), 214(1), 142-147. doi:http://dx.doi.org/10.1016/j.forsciint.2011.07.040

147. Lee, C., Stolk, R., Adler, A., Patel, A., Chalmers, J., Neal, B et al. Association between alcohol consumption and diabetic retinopathy and visual acuity—the AdRem Study. Diabetic Medicine. 2010: 1130-1137.

148. Bansal, D., Gudala, K., Muthyala, H., Esam, H., Nayakallu, R., &Bhansali, A. Peripheral neuropathy in type-II diabetic patients attending diabetic clinics in Al-

Azhar University Hospitals, Egypt. Journal of Diabetes Investigation. 2014:714-721.

149. Baldacchino S, Camilleri L, Fava S, et al. Risk Assessment Models for the Development of Complications in Maltese Type 2 Diabetic Patients. J Diabetes Metab. 2013; 4(2): 1-6

150. Preeti PP, Thanpi RR, Renish RK, Resmi RU, Vivek MR. Prevalence and risk factors of diabetic peripheral neuropathy among type-2 diabetic patients presenting to Smims Hospital, Tamil Nadu. Int J Med Scie Pub Health. 2013;2(2): 73-76.

151. Stoner, G. (2005). Hyperosmolar hyperglycemic state. Am Fam Physician., 71(9), 1723-1730.

152. Tchistiakova E, Anderson ND, Greenwood CE, MacIntosh BJ. Combined effects of type 2 diabetes and hypertension associated with cortical thinning and impaired cerebrovascular reactivity relative to hypertension alone in older adults. NeuroImage: Clinical. 2014; 5: 36–41.

153. Ostchega, Y., Paulose-Ram, R., Dillon, C. F., Gu, Q., & Hughes, J. P. (2007). Prevalence of peripheral arterial disease and risk factors in persons aged 60 and older: data from the National Health and Nutrition Examination Survey 1999–2004. J Am GeriatrSoc, 55, 583-589.

154. Singer, D. R. J., & Kite, A. (2008). Management of hypertension in peripheral arterial disease: Does the choice of drugs matter? European Journal of Vascular and Endovascular Surgery, 35(6), 701-708.

155. Deeter, K. H., Roberts, J. S., Bradford, H., Richards, T., Shaw, D., Marro, K., …Vavilala, M. S. (2011). Hypertension despite dehydration during severe pediatric

diabetic ketoacidosis. Pediatr Diabetes, 12(4 Pt 1), 295-301. doi: 10.1111/j.1399-5448.2010.00695.x

156. Kasim, K., Amar, M., Sadek, A., & Gawad, S. Peripheral neuropathy in type-II diabetic patients attending diabetic clinics in Al-Azhar University Hospitals, Egypt. International Journal of Diabetes Mellitus. 2010: 20-23.

157. Cho, D. Y., Mold, J. W., & Roberts, M. (2006). Further investigation of the negative association between hypertension and peripheral neuropathy in the elderly: An Oklahoma Physicians Resource/Research Network (OKPRN) study. J Am Board Fam Med., 19(3), 240-250. doi: 10.3122/jabfm.19.3.240

158. Jannot, M. F., Raccah, D., de La Tour, D. D., Coste, T., Gouvernet, J., & Vague, P. (1999). Relationship between neuropathy, hypertension and red blood cell Na/K ATPase in patients with insulin-dependent diabetes mellitus. Diabetes & Metabolism, 25(1), 35. doi: DM-05-1999-25-1-1262-3636-101019-ART58

159. Long, A. N., &Dagogo-Jack, S. (2011). Comorbidities of diabetes and hypertension: Mechanisms and approach to target organ protection. The Journal of Clinical Hypertension, 13(4), 244-251.

160. Bamashmoos MA, Ganem Y. Diabetic Nephropathy and its Risk Factors in Type 2-Diabetic Patients in Sana'a City, Yemen. World J Med Sci. 2013; 9 (3): 147-152.

161. Chang, Y., Chang, D., Lin, K., H. C., & Lee, Y. High-density lipoprotein cholesterol and the risk of nephropathy in type 2 diabetic patients. Nutrition, Metabolism, and Cardiovascular Diseases.2013:23(8);751-757.

162. Morton J, Zoungas S, Li Q, et al. Low HDL Cholesterol and the Risk of Diabetic Nephropathy and Retinopathy. Diabetes Care. 2012; 35(11): 2201-2206.

163. Wang S, Wang L, Zhou Y, et al. Prevalence and control of dyslipidaemia among diabetic patients with microalbuminuria in a Chinese hospital. Diabetes Vascular Dis Res. 2012;10(2): 169–178.

164. Yadav N, Shete AN, Khan ST. Effect of Hyperlipidemia on Nerve Conduction Velocity in Type II Diabetes Mellitus. JDMS. 2014; 13(5): 7-9.

165. Hahn, S. J., Park, J., Lee, J. H., Lee, J. K., & Kim, K.-A. (2010). Severe hypertriglyceridemia in diabetic ketoacidosis accompanied by acute pancreatitis: Case report. J Korean Med Sci., 25(9), 1375-1378. doi: 10.3346/jkms.2010.25.9.1375

166. Seth, A., Rajpal, S., Saigal, T., Bienvenu, J., Sheth, A., Alexander, J. S., … Jordan, P. A. (2014). Diabetic Ketoacidosis-induced hypertriglyceridemic acute pancreatitis treated with plasmapheresis—recipe for biochemical disaster management. Clin Med Insights Gastroenterol. 7, 51-53. doi: 10.4137/CGast.S18557

167. Khoury, J. F., King, D. A., Braun, E., &Naffaa, M. E. (2014). Unusual case of diabetic ketoacidosis. Case Reports in Internal Medicine, 2(1), 96-100.

168. Singla, A. A., Ting, F., & Singla, A. (2015). Acute pancreatitis secondary to diabetic ketoacidosis induced hypertriglyceridemia in a young adult with undiagnosed type 2 diabetes. JOP. J Pancreas (Online), 16(2), 201-204.

169. Al-Kaabi, J., Maskari, F., Zoubeidi, T., &Abdulle. Prevalence and Determinants of Peripheral Neuropathy in Patients with Type 2 Diabetes Attending a Tertiary Care Center in the United Arab Emirates. Journal of Diabetes & Metabolism. 2014a

170. Gosmanov, A. R., Gosmanova, E. O., &Kitabchi, A. E. (2015). Hyperglycemic crises: Diabetic ketoacidosis (DKA), and hyperglycemic hyperosmolar state (HHS). Retrieved from http://www.ncbi.nlm.nih.gov/books/NBK279052/

171. Gunton JE, Davies L, Wilmshurst E, Fulcher G, McElduff A. Cigarette smoking affects glycemic control in diabetes. Diabetes Care. 2002; 25(4): 796-797.

172. Hammes, H., Welp, R., Kempe, H., Wagner, C., Siegel, E., &Holl, R. Risk Factors for Retinopathy and DME in Type 2 Diabetes—Results from the German/Austrian DPV Database. PLOS One.2015.

173. Blomster, J., Woodward, M., Zoungas, S., Hillis, G., Harrap, S., Neal, B et al. The harms of smoking and benefits of smoking cessation in women compared with men with type 2 diabetes: an observational analysis of the ADVANCE (Action in Diabetes and Vascular Disease: Preterax and Diamicron modified release Controlled Evaluation) trial. BMJ. 2016.

174. Althouse, A. D., Brooks, M. M., Tyrrell, K. S., Abbott, J. D., &Forker, A. D. (2012). Abstract 11695: Risk factors for incident peripheral arterial disease in type 2 diabetes: Results from the bypass angioplasty revascularization investigation 2 diabetes (BARI 2D) trial. Circulation, 126, A11695.

175. Valdivielso, P., Ramírez-Bollero, J., & Pérez-López, C. (2014). Peripheral arterial disease, type 2 diabetes and postprandial lipidaemia: Is there a link? World J Diabetes, 5(5), 577-585. doi: 10.4239/wjd.v5.i5.577

176. Fernandez-Juarez, G., Luno, J., Barrio, V., de Vinuesa, S., Praga, M., Goioechea, M et al. 25 (OH) Vitamin D Levels and Renal Disease Progression in Patients with

Type 2 Diabetic Nephropathy and Blockade of the Renin-Angiotensin System. Clinical Journal of the American Society of Nephrology.2013: 1870-1876.

177. Alcubierre, N., Valls, J., Rubinat, E., Cao, G., Esquerda, A., Traveset, A et al. Vitamin D Deficiency Is Associated with the Presence and Severity of Diabetic Retinopathy in Type 2 Diabetes Mellitus. Journal of Diabetes Research. 2015: 1-7.

178. Diaz, V. A., Mainous, A. G., Carek, P. J., Wessell, A. M., Everett, C. J. (2009). The association of vitamin D deficiency and insufficiency with diabetic nephropathy: implications for health disparities. J Am Board Fam Med., 22(5), 521-527. doi: 10.3122/jabfm.2009.05.080231

179. Xiao, X., Wang, Y., Hou, Y., Han, F., Ren, J., &Hu, Z. (2016). Vitamin D deficiency and related risk factors in patients with diabetic nephropathy. J Int Med Res., 44(3), 673-84. doi: 10.1177/0300060515593765

180. Jung, C.-H., Kim, K.-J., Kim, C.-H., Kang, S., &Mok, J. Relationship between vitamin D status and vascular complications in patients with type 2 diabetes mellitus. Nutrition Research. 2016:117-124.

181. Anyanwu AC, Fasanmade OA, Odeniyi IA, et al. Effect of Vitamin D supplementation on glycemic control in Type 2 diabetes subjects in Lagos, Nigeria. Indian J EndocrinolMetab. 2016; 20(2): 189–194.

182. Enfield K, Shim M, Sharma G. Asthma, obesity and type 2 diabetes – mechanisms, management and prevention. Diab Care. 2009; 54(3): 30-33.

183. Black MH, Anderson A, Bell RA, et al. Prevalence of asthma and its association with glycemic control among youth with diabetes. Pediatrics. 2011;128:e839–e847.

184. Chance, W. W., Rhee, C., Yilmaz, C., Dane, D. M., Pruneda, M. L., Raskin, P., Hsia, C. C. (2008). Diminished alveolar microvascular reserves in type 2 diabetes reflect systemic microangiopathy. Diabetes Care, 31(8), 1596-601. doi: 10.2337/dc07-2323

185. Klein, O. L., Krishnan, J. A., Glick, S., & Smith, L. J. (2010). Systematic review of the association between lung function and Type 2 diabetes mellitus. Diabetic Medicine, 27(9), 977-987.

186. Hassan, J. Overview on Hyperlipidemia. J Chromat Separation Techniq. 2013; 4: e113.

187. Rosario, R. F., & Prabhakar, S. (2006). Lipids and diabetic nephropathy. Current Diabetes Reports, 6(6), 455-462.

188. Faruque, G. M., Ahsan, K., & Aim, A. (2008). Association of hyperlipidemia and diabetic retinopathy. J Dhaka Med Coll., 17(2), 62-66.

189. Larsson, L. I., Alm, A., Lithner, F., Dahlén, G., & Bergström, R. The association of hyperlipidemia with retinopathy in diabetic patients aged 15-50 years in the county of Umeå Acta Ophthalmol Scand., 77(5), 585-591.

190. Solanki JD, Makwana AH, Mehta HB, Gokhale PA, Shah CJ. A study of prevalence and association of risk factors for diabetic vasculopathy in an urban area of Gujarat. J Family Med Prim Care. 2013;2:360-

191. Hosmer Jr, D. W., & Lemeshow, S. (2004). Applied logistic regression. John Wiley & Sons.

192. King, G., & Zeng, L. (2001). Logistic regression in rare events data. Political analysis, 9(2), 137-163.

193. Kleinbaum, D. G., & Klein, M. (2010). Logistic regression: a self-learning text. Springer Science & Business Media.

194. Barros, A. J., & Hirakata, V. N. (2003). Alternatives for logistic regression in cross-sectional studies: an empirical comparison of models that directly estimate the prevalence ratio. BMC medical research methodology, 3(1), 1.

195. Zou, G. (2004). A modified poisson regression approach to prospective studies with binary data. American journal of epidemiology, 159(7), 702-706.

196. Vittinghoff, E., Glidden, D. V., Shiboski, S. C., & McCulloch, C. E. (2011). Regression methods in biostatistics: linear, logistic, survival, and repeated measures models. Springer Science & Business Media.

197. Didelez, V., & Sheehan, N. (2007). Mendelian randomization as an instrumental variable approach to causal inference. Statistical methods in medical research, 16(4), 309-330.

198. Lemon, S. C., Roy, J., Clark, M. A., Friedmann, P. D., & Rakowski, W. (2003). Classification and regression tree analysis in public health: methodological review and comparison with logistic regression. Annals of behavioral medicine, 26(3), 172-181.

199. Sauerbrei, W. (1999). The use of resampling methods to simplify regression models in medical statistics. Applied Statistics, 313-329.

200. Bewick, V., Cheek, L., & Ball, J. (2005). Statistics review 14: Logistic regression. Crit Care, 9(1), 112-118.

201. D'Agostino, R. B., Hamman, R. F., Karter, A. J., Mykkanen, L., Wagenknecht, L. E., & Haffner, S. M. (2004). Cardiovascular Disease Risk Factors Predict the

Development of Type 2 Diabetes The Insulin Resistance Atherosclerosis Study. Diabetes Care, 27(9), 2234-2240.

202. Martinsen, N., Jørgensen, M. E., Bjerregaard, P., Krasnik, A., Carstensen, B., & Borch-Johnsen, K. (2006). Predictions of type 2 diabetes and complocations in Greenland in 2014. International journal of circumpolar health, 65(3).

203. Li, C. P., Zhi, X. Y., Ma, J., Cui, Z., Zhu, Z. L., Zhang, C., & Hu, L. P. (2012). Performance comparison between Logistic regression, decision trees, and multilayer perceptron in predicting peripheral neuropathy in type 2 diabetes mellitus. Chinese medical journal, 125(5), 851-857.

204. Barski, L., Nevzorov, R., Harman-Boehm, I., Jotkowitz, A., Rabaev, E., Zektser, M., ... & Almog, Y. (2013). Comparison of diabetic ketoacidosis in patients with type-1 and type-2 diabetes mellitus. The American journal of the medical sciences, 345(4), 326-330.

205. Grover, G., Gadpayle, A. K., & Sabharwal, A. (2012). Identifying patients with diabetic nephropathy based on serum creatinine in the presence of covariates in type-2 diabetes: A retrospective study. Biomed Res India, 23(4), 1-11.

206. Yoo, T. K., & Park, E. C. (2013). Diabetic retinopathy risk prediction for fundus examination using sparse learning: a cross-sectional study. BMC medical informatics and decision making, 13(1), 106.

207. Baha, B. Y., and G. M. Wajiga. "Artificial neural networks to detect risk of type 2 diabetes." Journal of Research in National Development 10, no. 2 (2013): 120-125.

208. Shanker, Murali, M. Y. Hu, and M. S. Hung. "Estimating probabilities of diabetes mellitus using neural networks." SAR and QSAR in Environmental Research 11, no. 2 (2000): 133-147.

209. Divya, Ms, Raman Chhabra, Sumit Kaur, and Swagata Ghosh. "Diabetes detection using artificial neural networks & back-propagation algorithm."International Journal of Technology Enhancements and Emerging Engineering Research 2, no. 2 (2013): 9-11.

210. Gao, Wei, S. Y. Wang, Z. N. Wang, L. Y. Shi, and F. X. Dong. "[Study on the application of artificial neural network in analyzing the risk factors of diabetes mellitus]." Zhonghua liu xing bing xue za zhi= Zhonghua liuxingbingxue zazhi25, no. 8 (2004): 715-718.

211. Mohamed, Ehab I., R. Linder, G. Perriello, N. Di Daniele, S. J. Pöppl, and A. De Lorenzo. "Predicting Type 2 diabetes using an electronic nose-based artificial neural network analysis." Diabetes, nutrition & metabolism 15, no. 4 (2002): 215-221.

212. Goldfarb-Rumyantzev, Alexander S., and Lisa Pappas. "Prediction of renal insufficiency in Pima Indians with nephropathy of type 2 diabetes mellitus."American journal of kidney diseases 40, no. 2 (2002): 252-264.

213. Gardner, G. G., D. Keating, T. H. Williamson, and A. T. Elliott. "Automatic detection of diabetic retinopathy using an artificial neural network: a screening tool." British journal of Ophthalmology 80, no. 11 (1996): 940-944.

214. Mbirika, Douglas H. "A type-2 diabetes early warning system using particle swarm optimized artificial neural networks: a case of trans Nzoia county of Kenya." PhD diss., University of Nairobi, 2014.

215. Lipton, Zachary C., David C. Kale, Charles Elkan, and Randall Wetzell. "Learning to Diagnose with LSTM Recurrent Neural Networks." arXiv preprint arXiv:1511.03677 (2015).

216. Moghtaderi, Ali, Roya Alavi-Naini, Mehdi Mohammadi, and Homayra Rashidi. "Diabetic Neuropathy: Determining the Sensitivity of Peripheral Nerves During a Short Course of Glycémie Control." J. Med. Sci 6, no. 5 (2006): 818-822.

217. Thongboonkerd, Visith, ed. Proteomics in Nephrology: Towards Clinical Applications. Vol. 160. Karger Medical and Scientific Publishers, 2008.

218. Agresti, A. (1996). *Categorical data analysis*. New York: John Wiley & Sons.

219. Ahmad, Z., &Saleem, A. (2012). Predicting Level of Development for Different Countries. *Journal of Sustainable Development*, *5*(11), 15.

220. Gershenson, C. (2003). Artificial neural networks for beginners. *arXiv preprint cs/0308031*.

221. Hanley, J. A & McNeil, B. J. (1892). The Meaning and Use of the Area under a Receiver Operating Characteristic (ROC) curve. *Radiology, 143*(1):29-36.

222. Hair, J. F., Black, W. C., Babin, B. J., Anderson, R. E., & Tatham, R. L. (2006). *Multivariate data analysis* (Vol. 6). Upper Saddle River, NJ: Pearson Prentice Hall.

223. Kamruzzaman, J., Begg, R. & Sarker, R. (2006). *Overview of Artificial Neural Networks and Their Applications in Healthcare.* New York: IGI Global.

224. Lisboa, P. J. & Taktak, A. F. (2006). The Use of Artificial Neural Networks in Decision Support in Cancer: A Systematic Review. *Neural networks : the official journal of the International Neural Network Society, 19*(4):408-415.

225. Micheli-Tzanakou E. (2011). Artificial Neural Networks: An Overview. *Network: Computation in Neural Systems, 22*(1-4):208-230.

226. Narayan, K. M., Boyle, J. P., Geiss, L. S., Saaddine, J. B. & Thompson, T. J. (2006). Impact of recent increase in incidence on future diabetes burden: U.S., 2005-2050. *Diabetes Care, 29,* (2006):2114–211

227. Scheaffer, R. L., & Yes, N. (1999). Categorical data analysis. *NCSSM Statistics Leadership Institute*.