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Review Article

Complications Associated with Type 2 Diabetes Mellitus, Pathophysiology, Diagnosis and Management: A Concise Review of Current Literature

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Abstract

Diabetes Mellitus, a chronic metabolic disease caused by defective insulin secretion by pancreatic β-cells or the inability of insulin-sensitive tissues to respond to insulin, is on the rise globally, particularly in low-middle income countries, leading to complications. Chronic hyperglycemia in DM is associated with organ and tissue damage, malfunction, and failure, as well as the development of microvascular (retinopathy, nephropathy, and neuropathy) and macrovascular (cardiovascular diseases) problems. As a result, this review x-rays the risk factors, aetiology, epidemiology, associated complications with key emphasis on the underlying mechanisms and pathophysiology, current laboratory diagnosis using conventional and novel biomarkers, as well as current trends in the management of type 2 diabetes mellitus (T2DM), highlighting the need for a combined approach in management viz-a-viz lifestyle management along with pharmacological approaches as crucial to achieving success.

Keywords: Diabetes Mellitus, Type 2 Diabetes Mellitus, Risk Factors, Aetiology, Epidemiology, Prevalence, Pathophysiology, Associated Complications, Diagnosis, Biomarkers, Management of T2DM.

1.0 INTRODUCTION

Diabetes mellitus is taken from the Greek word diabetes, meaning siphon - to pass through and the Latin word mellitus meaning sweet. A review of the history shows that the term "diabetes" was first used by Apollonius of Memphis around 250 to 300 BC. Ancient Greek, Indian, and Egyptian civilizations discovered the sweet nature of urine in this condition, and hence the propagation of the word Diabetes Mellitus came into being. Mering and Minkowski, in 1889, discovered the role of the pancreas in the pathogenesis of diabetes (Sapra and Bhandari, 2021).

The World Health Organization (WHO) defines diabetes mellitus as a chronic, metabolic disease characterized by elevated levels of blood glucose, which leads over time to damage to the heart, vasculature, eyes, kidneys and nerves (Roden and Shulman, 2019). There are basically three types of diabetes: type 1 diabetes mellitus, type 2 diabetes mellitus and gestational diabetes mellitus. Type 1 diabetes usually develops early in life, and has been known previously as insulin-dependent or juvenile diabetes. It is most common in African Americans and Hispanics/Latinos. Type 2 was formerly called non-insulin dependent diabetes mellitus (NIDDM). It is basically lifestyle dependent. Risk factors for developing type 2 diabetes include family history, aging and being overweight or obese, though as youth obesity rates rise, so do cases of early-onset Type 2 diabetes (Ogbodo *et al*., 2024; Ogbodo *et al*., 2023; Ezeugwunne *et al*., 2017). While diabetes and the complications of it is the number 7 cause of death in the United States, it has a much higher mortality rate in the rest of the world (Roden and Shulman, 2019). This is especially true in middle- to low-income countries, as these countries are often unable to access proper treatment for this condition.

1.1 Background on Diabetes Mellitus (DM)

Diabetes is a chronic, metabolic disease characterized by elevated levels of blood glucose (or blood sugar), which leads over time to serious damage to the heart, blood vessels, eyes, kidneys and nerves. The most common is type 2 diabetes, usually in adults, which occurs when the body becomes resistant to insulin or does not make enough insulin. In the past three decades the prevalence of type 2 diabetes has risen dramatically in countries of all income levels (WHO, 2022). Type 1 diabetes, once known as juvenile diabetes or insulin-dependent diabetes, is a chronic condition in which the

pancreas produces little or no insulin by itself. For people living with diabetes, access to affordable treatment, including insulin, is critical to their survival. About 422 million people worldwide have diabetes, the majority living in low-and middle-income countries, and 1.5 million deaths are directly attributed to diabetes each year. Both the number of cases and the prevalence of diabetes have been steadily increasing over the past few decades (WHO, 2022). Type 2 diabetes is recognized as a serious public health concern with a considerable impact on human life and health expenditures. Rapid economic development and urbanization have led to a rising burden of diabetes in many parts of the world (Onyango and Onyango, 2018). Diabetes affects individuals' functional capacities and quality of life, leading to significant morbidity and premature mortality (Ramtahal *et al.,* 2015). Recently, concerns have been raised that more than one-third of the diabetes-related deaths occur in people under the age of 60 (Alotaibi *et al*., 2017). Increased consumption of unhealthy diets and sedentary lifestyles, resulting in elevated Body Mass Index (BMI) and fasting plasma glucose, have been blamed for these trends (Lone *et al.,* 2017). In particular, persons with higher BMI are more likely to have type 2 diabetes. The aging of the human population is another contributor, as diabetes tends to affect older individuals. The cost of diabetes care is at least 3.2 times greater than the average per capita healthcare expenditure, rising to 9.4 times in presence of complications. Control of blood glucose, blood pressure, and other targets remains suboptimal for many patients (Al Slail *et al.,* 2016). This has been partly attributed to the lack of awareness and health promotion needed for diabetes control.

2.1 Type 2 DM

Diabetes is a chronic metabolic disease that occurs either when the pancreas does not produce enough insulin or when the body cannot effectively use the insulin it produces (ogbodo *et al*., 2019). Insulin is a hormone that regulates blood sugar (WHO, 2021). Type 2 Diabetes Mellitus (T2DM) is one of the most common metabolic disorders worldwide and its development is primarily caused by a combination of two main factors: defective insulin secretion by pancreatic β-cells and the inability of insulin-sensitive tissues to respond to insulin (Roden Shulman, 2019). Insulin release and action have to precisely meet the metabolic demand; hence, the molecular mechanisms involved in the synthesis and release of insulin, as well as the insulin response in tissues must be tightly regulated. Therefore, defects in any of the mechanisms involved can lead to a metabolic imbalance that leads to the pathogenesis of T2DM. Over 90% of diabetes mellitus cases are type 2 diabetes mellitus (T2DM), a condition marked by deficient insulin secretion by pancreatic islet β-cells, tissue insulin resistance (IR) and an inadequate compensatory insulin secretory response (Stumvoll *et al*., 2005). Progression of the disease makes insulin secretion unable to maintain glucose homeostasis, producing hyperglycaemia. Patients with T2DM are mostly characterized by being obese or having a higher body fat percentage, distributed predominantly in the abdominal region. In this condition, adipose tissue promotes IR through various inflammatory mechanisms, including increased free fatty acid (FFA) release and adipokine deregulation. Combinational therapies employed after failure of monotherapy result in comorbidities.

2.1.1 Aetiology of Type 2 DM

Type 2 diabetes is a multifactorial disorder that leads to a disturbed glucose homeostasis. Complex interplays between genetics and environmental factors play important roles in the development of diabetes (Borse *et al*., 2021).

Glucose is a key energy source for all cells in our body. It is derived directly from the food we eat (digestion and absorption), and is also supplied by the liver - either by breakdown of glycogen stores (glycogenolysis) or synthesis of glucose using other building blocks (gluconeogenesis). Insulin causes skeletal muscle and lipid cells in our body to take up glucose from the blood. Another hormone, glucagon, counters the insulin function and facilitates glucose production during periods of starvation.

Absence, inadequate supply, and improper function of insulin are some of the primary causes of diabetes. Causes of diabetes are also used to classify the types of diabetes. For example:

Absence of Insulin: Pancreatic cells producing insulin are selectively destroyed by an autoimmune response, leading to Type 1 diabetes.

Insulin Resistance: The individual may either have inadequate quantities of insulin in the body or problems with insulin function, both leading to Type 2 diabetes.

- Inadequate insulin supply: Weight gain and obesity can lead to imbalance in the amount of insulin in relation to sensitivity of the cells to insulin
- Improper insulin function: Insulin binds to its receptor and initiates a cascade of signals in the cell, ultimately leading to the uptake of glucose. Missing or defective proteins in the signaling cascade (due to genetic defects or mutations) and/or changes in metabolites or signaling molecules (such as high levels of free fatty acids) may disturb the metabolic balance, leading to diabetes.

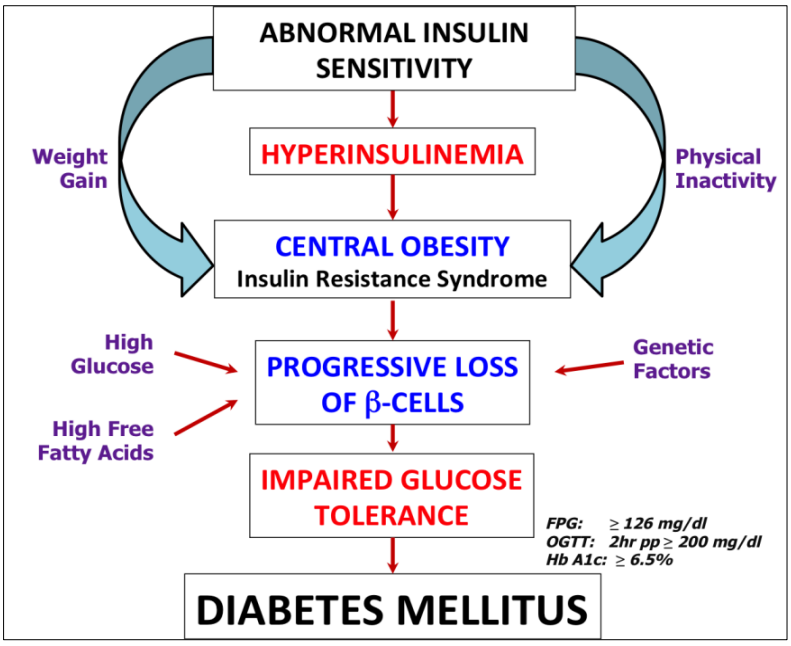

Fig.1: Some of the causes of Diabetes mellitus (Jiang and Dutta, 2017)

2.2 Epidemiology of Type 2 DM

In 2017, approximately 462 million individuals were affected by type 2 diabetes corresponding to 6.28% of the world's population (4.4% of those aged 15-49 years, 15% of those aged 50-69, and 22% of those aged 70+), or a prevalence rate of 6059 cases per 100,000. Over 1 million deaths per year can be attributed to diabetes alone, making it the ninth leading cause of mortality (Khan *et al.,* 2020). The burden of diabetes mellitus is rising globally, and at a much faster rate in developed regions, such as Western Europe. The gender distribution is equal, and the incidence peaks at around 55 years of age. Global prevalence of type 2 diabetes is projected to increase to 7079 individuals per 100,000 by 2030, reflecting a continued rise across all regions of the world. There are concerning trends of rising prevalence in lower-income countries. Urgent public health and clinical preventive measures are warranted (Khan *et al.,* 2020).

The incidence of type 2 DM varies substantially from one geographical region to the other as a result of environmental and lifestyle risk factors. Literature search has shown that there are few data available on the prevalence of type 2 DM in Africa as a whole. Studies examining data trends within Africa point to evidence of a dramatic increase in prevalence in both rural and urban setting, and affecting both gender equally (Mbanya, 2007). The majority of the DM burden in Africa appears to be type 2 DM, with less than 10% of DM cases being type 1 DM (Mbanya, 2007). In Nigeria, the current prevalence of DM among adults aged 20–69 years is reported to be 1.7%]. It is widely perceived that prevalence figures reported by the International Diabetes Federation (IDF) grossly under-report the true burden of DM in Nigeria, given that they are derived through the extrapolation of data from other countries (International Diabetes Federation, 2017). It is predicted that the prevalence of DM in adults of which type 2 DM is becoming prominent will increase in the next two decades and much of the increase will occur in developing countries where the majority of patients are aged between 45 and 64 years. It is projected that the latter will equal or even exceed the former in developing nations, thus culminating in a double burden as a result of the current trend of transition from communicable to non-communicable diseases (Yach *et al.*, 2004).

2.3 Prevalence Rate of Diabetes Mellitus

The global diabetes prevalence in 2019 is estimated to be 9.3% (463 million people), rising to 10.2% (578 million) by 2030 and 10.9% (700 million) by 2045. The prevalence is higher in urban (10.8%) than rural (7.2%) areas, and in high-income (10.4%) than low-income countries (4.0%). One in two (50.1%) people living with diabetes do not know that they have diabetes. In 2014, 8.5% of adults aged 18 years and older had diabetes. In 2019, diabetes was the direct cause of 1.5 million deaths and 48% of all deaths due to diabetes occurred before the age of 70 years. Between 2000 and 2016, there was a 5% increase in premature mortality rates (i.e. before the age of 70) from diabetes. In high-income countries the premature mortality rate due to diabetes decreased from 2000 to 2010 but then increased in 2010-2016. In lower-middle-income countries, the premature mortality rate due to diabetes increased across both periods. By contrast, the probability of dying from any one of the four main noncommunicable diseases (cardiovascular diseases, cancer, chronic respiratory diseases or diabetes) between the ages of 30 and 70 decreased by 18% globally between 2000 and 2016 (WHO, 2021). According to International Diabetes Federation (IDF, 2021), about 24 million adults between the ages of 20-79 are living with diabetes in Africa. This

figure is estimated to increase to 33 million by 2030 and 55 million by 2045. About 52 million adults (20-79) in the IDF Africa Region have impaired glucose tolerance (IGT) which places them at high risk of developing type 2 diabetes. This figures are estimated to reach 71 million by 2030 and 117 million by 2045. About 13 million adults living with diabetes in the IDF Africa Region are undiagnosed - 54% of the total number of adults with diabetes in the region. Diabetes is responsible for 416,000 deaths in the IDF Africa Region in 2021. About 1 in 8 live births in the IDF Africa Region are affected by hyperglycaemia in pregnancy (IDF, 2021).

Nigeria is one of the countries in sub-Saharan Africa (SSA) that are currently groaning under a rising prevalence of diabetes mellitus (DM). A recent meta-analysis reported that approximately 5.8% (about 6 million) of adult Nigerians are living with DM (Uloko *et al*., 2018). This figure has been likened to a tip of an iceberg as it is estimated that two-thirds of diabetes cases in Nigeria are yet undiagnosed (International Diabetes Federation, 2017). This scenario which applies to most low and middle income countries of SSA has not only resulted to an increase in the burden of diabetes complications and deaths, but has also put a significant strain on the already weak health systems in this sub-region.

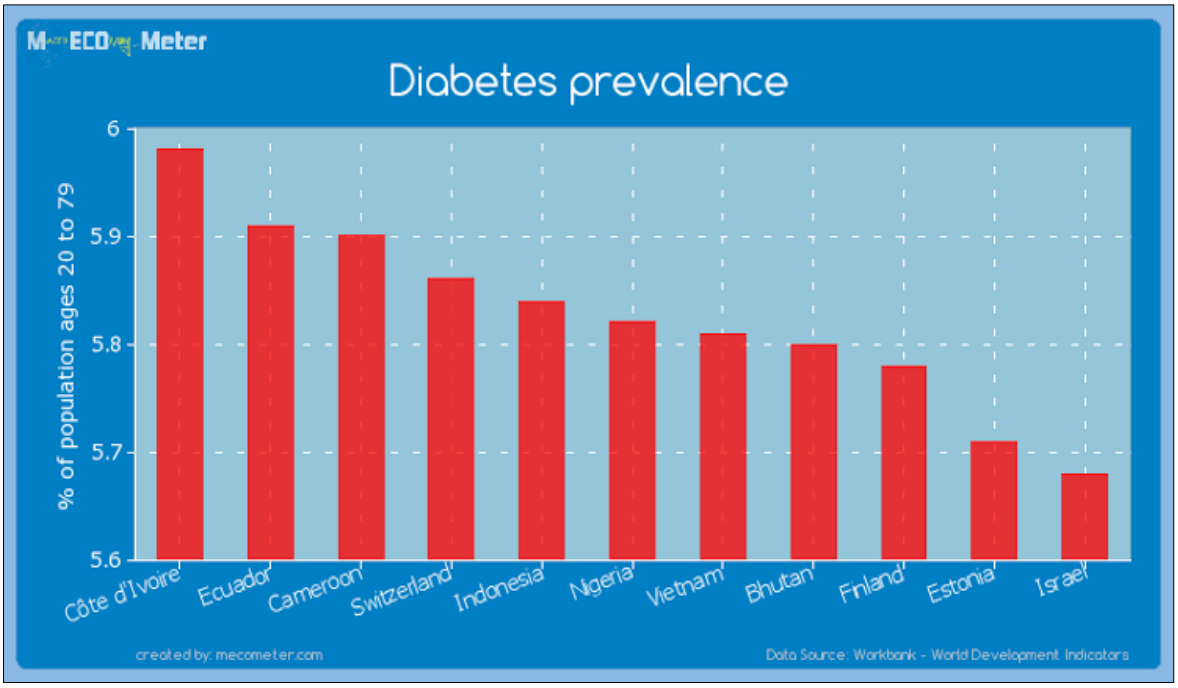

Fig. 2: Prevalence rate of Diabetes mellitus in different parts of the world (World Development Indicators, 2021)

2.4 Pathogenesis of Type 2 DM

Typically, T2DM does not manifest acutely in individuals but is preceded by an insidious phase of pre-diabetes (Bansal, 2015). Prediabetes is characterised by raised blood glucose levels (fasting plasma glucose levels of 6.1-6.9 mmol/L and two hours post glucose ingestion levels between 7.8-11 mmol/L) due to declining islet beta-cell mass and function but not enough to warrant a diagnosis of T2DM (Tabák *et al.*, 2012). Patients with prediabetes are asymptomatic but about 5-10% progress to T2DM each year. Studies have demonstrated that weight loss and exercise can usually delay progression to T2DM, or even prevent T2DM from manifesting; lifestyle interventions reduce the risk of T2DM progression in 40-70% of adults with pre-diabetes (Tabák *et al.*, 2012). It has been estimated that around 70% of individuals with persistent prediabetes will eventually develop T2D, and that more than 470 million people will have prediabetes by 2030 (Tabák *et al.*, 2012). Progressing to T2DM is characterised by blood glucose levels of greater than 7 mmol/L during fasting and a two hours post glucose ingestion reading of more than 11 mmol/L (Bansal, 2015). The consensus in the literature is that T2DM clinical manifestation is provoked by peripheral tissue insulin resistance, which is in turn, usually induced by obesity (Affourtit, 2016). Obesity is characterised by elevated levels of cytokines and fatty acids, and it is thought that elevated levels of both provoke insulin resistance (Affourtit, 2016). Following the induction of insulin resistance, islet beta-cells can maintain normoglycaemia and metabolic homeostasis by increasing their secretion of insulin and/or by increasing their number (Linnemann *et al.*, 2014). Obesity has been estimated to induce around 50% increase in islet beta-cell volume due to increased neogenesis (Fonseca, 2009). However, over time islet beta-cells are seemingly unable to compensate for the insulin resistance and their ability to secrete insulin decreases and many islet beta-cells undergo apoptosis, which is thought to be a result of a variety of stressors, such as increased insulin demand, oxidative, endoplasmic reticulum, dyslipidemic, amyloidal, and

inflammatory stress (Boland *et al.*, 2017). The characteristic consequences of beta-cell pathology during T2DM include impaired first-phase insulin secretion, ongoing insufficient insulin secretion to promote normolipidaemia (normal triglyceride levels, normal LDL cholesterol, and normal HDL-cholesterol) and normoglycaemia, dysfunctional glucose-sensing, and an increased proportion of proinsulin secretion (Boland *et al.*, 2017). During prediabetes, pancreatic beta-cell number and function decline slowly, usually over a few years before T2DM manifests (Tabák *et al.*, 2012). It has been reported that the decline in islet beta-cell function can begin an average of 12 years before T2DM diagnosis (Affourtit, 2016). Interestingly, there have been reports of individuals who do not progress to T1D for more than 10 years despite persistent islet autoimmunity (slow progressors). This demonstrates that the rate of islet beta-cell death can vary greatly between individuals before T1D or T2DM diagnosis, enabling some individuals to remain disease-free for longer, possibly by similar mechanisms. The gradual decline in islet beta-cell number and function results in insulin levels becoming too low to promote metabolic homeostasis and T2DM results (Tabák *et al.*, 2012). Hyperproinsulinemia has been reported in both T2DM patients and individuals with prediabetes, suggesting that defective islet beta-cell insulin processing is integral to the early stages of disease pathology (Yoshino *et al.*, 2021; *Pfützner et al., 2015; Breuer et al., 2010*).

2.4.1 Amylin Proteins and Pancreatic β-Cell Function

β-Cells are the most extensively studied pancreatic cells for their roles in glucose homeostasis in T2DM. Islet amyloid PP (amylin) is a β-cell peptide hormone that is secreted along with insulin in the ratio of approximately 100:1. Its secretion is also altered in diabetic patients. Amylin functions as an inhibitor of glucagon secretion and delays gastric emptying thus acting as a satiety agent (Schmitz *et al.,* 2004). Amylin action is executed through an area postrema (glucose-sensitive part of the brain stem) that collectively aims to reduce the demand of total insulin. Besides these functions, amylin also plays roles in the destruction of β-cell via the formation of amyloid aggregates and fibers. Findings from histopathology have shown the accumulation of extracellular amyloid proteins, hyperphosphorylated tau, ubiquitin, apolipoprotein E, apolipoprotein (a), c-Jun N-terminal kinases (JNK1), and islet-brain 1/JNK1 interacting protein-1 (IB1/JIP-1) as the characteristic feature of pancreatic islets in T2DM individuals, suggesting that amylin in association with endocrine system plays important roles in physiology, pathology, and progression of T2DM (Miklossy *et al.,* 2010).

2.4.2 α-Cells

α-cells are known to play crucial roles in the pathophysiology of T2DM. The secretion of glucagon from α-cell is regulated by glucose, hormones, and other substrates that work in unison. Any abnormality in α-cells is reflected in altered glucose homeostasis (Jacobson *et al.*, 2009). In T2DM, a relative elevated secretion of glucagon takes place in fasting and postprandial states during normal and increased glucose levels along with altered hypoglycemic response. According to the bi-hormonal hypothesis, T2DM is the consequence of insulin resistance/deficiency with a relative excess glucagon secretion, leading to a rate of hepatic glucose production that is much higher than the rates of glucose utilization. This consequently results in hyperglycemia. The hypothesis is supported by a plethora of clinical and experimental investigations (Dunning and Gerich, 2007). Reduced suppression of glucagon release under hyperglycemic conditions is a contributing factor to postprandial hyperglycemia (Shah *et al*., 2000). Interestingly, α-cells do not show this behavior in the presence of adequate insulin levels, suggesting that impairment in insulin machinery also cause the abnormalities in glucagon release in T2DM. In addition to this, hypoglycemia is remarkably influenced by glucagon secretion in T2DM patients treated with insulin. In such patients, the secretory response of α-cells to low-glucose concentrations is compromised, which further aggravates the risks of severe hypoglycemia (Cryer, 2002). The deficiency of glucagon action in response to hypoglycemia is linked with multiple failures in α-cell regulation (Zhou *et al.,* 2007). Even in the situation of islet allotransplantation that helps diabetes patients to remain independent to insulin for a long time, the retarded response of α-cell response to hypoglycemia usually remains unaffected, indicating that the procedure does not completely restore the physiological functions of α-cells (Paty *et al.,* 2002). Collectively, defects in α-cell regulation and glucagon secretion lead to defective glucose sensing, loss of β-cell function, and insulin resistance.

2.5 Risk Factors That Predispose To Development of Type 2 DM

The risk factors associated with T2DM include a complex combination of genetic, metabolic and environmental factors that interact with one another contributing to its prevalence. Although individual predisposition to T2DM due to non-modifiable risk factors (ethnicity and family history/genetic predisposition) has a strong genetic basis, evidence from epidemiological studies suggests that many cases of T2DM can be prevented by improving the main modifiable risk factors (obesity, low physical activity and an unhealthy diet) (Schellenberg *et al.,* 2013). The main drivers of the T2DM epidemic are the global rise in obesity, sedentary lifestyles, high caloric diets, population aging and family history of diabetes, which have quadrupled the incidence and prevalence of T2DM (Okwara *et al*., 2021; Chatterjee *et al.*, 2017; Ezeugwunne *et al*., 2017). Other factors include; old age, high blood pressure, impaired glucose tolerance (IGT), history of gestational diabetes, poor nutrition during pregnancy (Ogbodo *et al*., 2023; Ogbodo *et al*., 2024c).

2.5.1 Ethnicity and Family History/Genetic Predisposition

Globally, the incidence and prevalence of T2DM are found to vary widely depending on ethnicity and geographical region with Japanese, Hispanics and Native Americans having the highest risks (Liu *et al.*, 2009). It has been shown higher incidence rates in Asians compared with a White American population and white population in the UK, where the highest risk is among the black population (Haines *et al.,* 2007). Whilst no clear reasons have been found, contributing factors such as modern lifestyle factors (which promote obesity), socioeconomic and direct genetic propensity or gene environmental interactions have been postulated. Genetic predisposition plays an important part in the risk of developing T2DM. Over the past decade, several T2DM genome-wide association studies have shown the complex polygenic nature of T2DM in which most of these loci increase T2DM risk through primary effects on insulin secretion, and a minority act through reducing insulin action (Fuchs berger *et al.,* 2016). Dimas *et al.* (2014) grouped these variants on the basis of their potential intermediate mechanisms in T2DM pathophysiology, with four variants fitting a clear IR pattern; two reducing insulin secretion with fasting hyperglycemia; nine lowering insulin secretion with normal fasting glycemia; and one altering insulin processing. According to these data, the genetic architecture of T2DM is highly polygenic, and additional association studies are needed to identify most T2DM loci (Flannick and Florez, 2016). Interactions between susceptibility loci and environmental factors could underlie the missing heritability of T2DM thus the impact of a given genetic variant can be modulated by the environmental factors (and vice versa) as evidenced by both observational studies and clinical trials (Franks *et al.,* 2013).

2.5.2 Obesity, Low Physical Activity and Unhealthy Diet

Obesity (body-mass index [BMI]≥30 kg/m2) is the strongest risk factor for T2DM (Bellou *et al.,* 2018) and is associated with metabolic abnormalities resulting in insulin resistance (IR). There exist an inverse linear relationship between BMI and the age at diagnosis of T2DM (Hillier and Pedula, 2003). The exact mechanisms by which obesity induces T2DM and IR remain to be elucidated; however, numerous factors have shown a significant role in the development of this pathological process, which involves both cell-autonomous mechanisms and inter-organ communications.

Obesity

Type 2 diabetes and obesity are associated with insulin resistance. Most obese individuals, despite being insulin resistant, do not develop hyperglycemia. Pancreatic β-cells of the islet of Langerhans release adequate amounts of insulin that are sufficient to overcome insulin level reductions under normal circumstances, thus maintaining normal glucose tolerance. Throughout the natural history of type 2 diabetes, endothelial dysfunction is accompanied with obesity/insulin resistance in diabetes and prediabetes conditions (this includes people with impaired glucose tolerance and/or impaired fasting glucose). In order to develop insulin resistance and obesity, thereby causing type 2 diabetes, β-cells should not be able to compensate fully for decreased insulin sensitivity. The nonesterified fatty acids (NEFAs) that are secreted from adipose tissue in obese people may lead to the hypothesis that insulin resistance and β-cell dysfunction are most likely linked (Kahn *et al.,* 2004).

Obesity and Insulin Resistance

Insulin sensitivity fluctuation occurs across the natural life cycle. For example, insulin resistance is noticed during puberty, in pregnancy, and during the aging process.25 In addition, lifestyle variations, such as increased carbohydrate intake and increased physical inactivity, are associated with insulin sensitivity fluctuations (Kasuga, 2006). Obesity is considered the most important factor in the development of metabolic diseases. Adipose tissue affects metabolism by secreting hormones, glycerol, and other substances including leptin, cytokines, adiponectin, and proinflammatory substances, and by releasing NEFAs. In obese individuals, the secretion of these substances will be increased (Karpe *et al.*, 2011). The cornerstone factor affecting insulin insensitivity is the release of NEFAs. Increased release of NEFAs is observed in type 2 diabetes and in obesity, and it is associated with insulin resistance in both conditions (Jelic *et al.*, 2007). Shortly after an acute increase of plasma NEFA levels in humans, insulin resistance starts to develop. Conversely, when the level of plasma NEFA decreases, as in the case with antilipolytic agent use, peripheral insulin uptake and glucose monitoring will be improved (Jelic *et al.,* 2007). Insulin sensitivity is determined by another critical factor, which is body fat distribution. Insulin resistance is associated with body mass index at any degree of weight gain. Insulin sensitivity also differs completely in lean individuals because of differences in body fat distribution. Individuals whose fat distribution is more peripheral have more insulin sensitivity than do individuals whose fat distribution is more central (in the abdomen and chest area) (Karpe *et al*., 2011).

Obesity and β-Cell Dysfunction

β-cells play a vital role in regulating insulin release, despite their fragility. The quantity of insulin released by β-cells fluctuates and changes according to the quantity, nature, and route of administration of the stimulus. Therefore, β-cells play a very important role in ensuring that in healthy subjects, concentrations of blood glucose are stable within a relatively normal physiological range. In obesity, insulin sensitivity, as well as the modulation of β-cell function, decreases. Insulin-resistant individuals, whether slim or fat, have more insulin responses and lower hepatic insulin

clearance than those who are insulin sensitive. In a normal healthy subject, there is a continuous feedback relationship between the β-cells and the insulin-sensitive tissues (Kasuga, 2006). If the adipose tissue, liver, and muscles demand glucose, this will lead to increased insulin supply by the β-cells. If the glucose levels require stability, changes in insulin sensitivity must be matched by a relatively opposite change in circulating insulin levels. Failure of this process to take place results in a deregulation of glucose levels and the development of DM. If the β-cells are healthy, there is an adaptive response to insulin resistance, which leads to the maintenance of normal levels of glucose. By contrast, when pancreatic β-cells are impaired, abnormal glucose tolerance or abnormal fasting glucose may develop, and it may even be followed by the development of type 2 diabetes.

Low Physical Activity

Insufficient physical activity (PA) is now an important topic in healthcare education, especially in the context of noncommunicable diseases (NCDs) because of the high risk for cardiovascular and metabolic diseases (Moholdt *et al.,* 2008). The absence of PA is also considered an urgent public health problem worldwide (Gonzalez *et al*., 2017). Previous research showed that insufficient PA is already a global public health concern and is increasing rapidly especially in low-income countries. A sedentary lifestyle is a known risk factor for T2DM as shown by the Women's Health Study and in the Kuipio Ischemic Heart Disease Risk Factor Study, which showed a reduction of 34% and 56% reduction of developing T2DM in participants walking 2-3 h a week or at least 40 min a week, respectively (Weinstein *et al.*, 2004). There are three primary benefits of physical activity on the delay of T2DM onset. First, the contraction of skeletal muscle cells induces an increase in blood flow into the muscle, enhancing glucose uptake from plasma. Second, physical activity reduces the notorious intra-abdominal fat, which is a known risk factor that promotes IR (Strasser, 2013). Finally, moderate-intensity exercise has been shown to improve glucose uptake by 40% (Ross, 2003). Physical activity improves glucose uptake and insulin sensitivity but it can also improve or even reverse inflammation and oxidative stress, which are T2DM predisposing factors. Human lifestyle has changed dramatically around the world as rapid economic development has occurred. Research showed that the prevalence of low PA among individuals aged 15 or older varied from 2.6% to 62.3% (Moholdt *et al.,* 2008). The available data indicated that low PA is increasing rapidly in developing countries. For the past few years, PA levels have been assessed using the Global PA Questionnaire (GPAQ) that is used for many epidemiologic studies of DM and cardiovascular outcomes worldwide (Xu *et al*., 2013).

Ethnicity

Type 2 diabetes mellitus is associated with substantial disease burden, including increased mortality risk and significant long-term morbidity (Diabetes UK, 2019). The global prevalence of diabetes in adults has increased considerably over the last decade; from 30 million in 1964 to more than 400 million in 2015, equivalent to 8.8% of the population aged between 20 and 79 years (Ogurtsova *et al*., 2017). However, there are substantial differences in the prevalence of diabetes at regional level, and in particular among different ethnic groups (Ogurtsova *et al*., 2017). There is widespread acceptance that the prevalence of type 2 diabetes is indeed higher among Asian, Black and minority ethnic (BME) groups in the UK (Goff, 2019). However, there are limited data available, and the last large-scale survey was conducted in the early 2000s. The 2004 Health Survey for England (HSfE) collected data from around 13,500 adults and suggested that the prevalence of type 2 diabetes was much higher in Black Caribbean (9.5% men, 7.6% women), Indian (9.2% men, 5.9% women), Pakistani (7.3% men, 8.4% women), and Bangladeshi (8.0% men, 4.5% women) than in the general population (3.8% men, 3.1% women) (NHS Digital, 2004). Compared with those of White ethnicity, the likelihood of having a type 2 diabetes diagnosis was more than double among Asian people, 65% more likely among Black people, and 17% more likely among people of Mixed/Other ethnicities, after adjustment for other demographic characteristics (Pham *et al*., 2019).

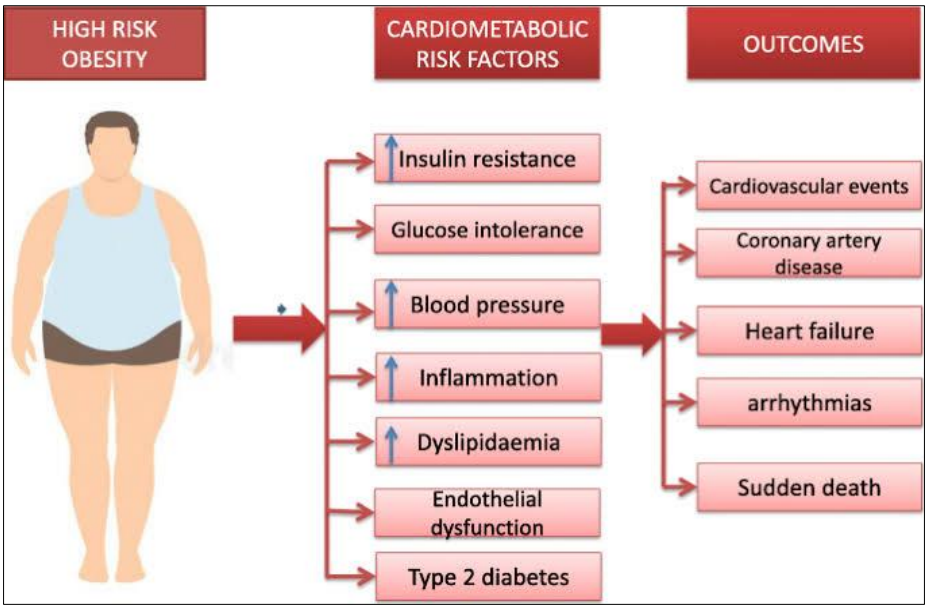

Fig. 3: Relationships between high-risk obesity, intermediate cardiometabolic risk factors, and cardiovascular outcomes (obesity phenotypes, diabetes, and cardiovascular diseases (Sharma *et al.*, 2020)

2.6 Complications Associated with Type 2 DM (Nephropathy, Retinopathy, Neuropathy etc.)

Chronic hyperglycemia in DM is accompanied by damage, dysfunction and failure of various organs and tissues, development of microvascular (retinopathy, nephropathy, and neuropathy) and macrovascular (cardiovascular disorders) complications (Harding *et al.*, 2019; Ihim *et al*., 2019; Analike *et al*., 2019; Ezeugwunne *et al*., 2021).

2.6.1 Microvascular Complications

These complications affect the vascular system causing damage to small blood vessels. They include;

2.6.1.1 Cataracts:

This is the loss of transparency of the crystalline lens and is divided into: congenital or developmental and acquired or degenerative, which produces difficulty in vision by interfering with movements ordered by light rays, diplopia, poor night vision (International council of Ophthalmology, 2015). People with diabetes may be twice as likely to develop cataracts as those without diabetes. Cataracts are cloudy areas in the lens of the cornea that blur vision. People with diabetes can experience damage to blood vessels in the eyes from high blood sugar and swelling in the liquid between the eyeball and cornea lens (Eagle, 2021).

Risk Factors for Cataracts in People with Diabetes

The main risk factors for people with diabetes developing cataracts are older age, long duration of diabetes, and decreased metabolic control.

Symptoms of Cataracts

Cataracts form very slowly. A person can have an early-stage cataract without showing any symptoms.

The main signs and symptoms of a cataract include:

- cloudy or blurred vision
- spots or floaters in a person's vision
- reduced intensity of colors
- sensitivity to glare from lights, which can make driving at night difficult
- seeing a halo of light around lights
- yellowing of a person's vision
- Vision changes that require a change in eyeglass prescription (Eagle, 2021).

2.6.1.2 Glaucoma:

This is a group of diseases that cause damage to the optic nerve and lead to loss of vision due to increased intraocular pressure. The risk of blindness depends on: levels of intraocular pressure, severity of the disease, age of onset, family history (Labrada-Arias *et al.,* 2018). Three forms forms of glaucoma are common in type 2 diabetes mellitus- primary open-angle glaucoma, neovascular glaucoma and steroid-induced glaucoma (Yvonne, 2021). In diabetic patients who have primary open-angle glaucoma, the glaucoma is treated the same way as for non-diabetic patients with open-angle glaucoma by lowering the eye pressure with medications, laser, and surgery if needed. Neovascular glaucoma is another type of glaucoma for which diabetic patients are at higher risk. In this type of glaucoma, patients usually have a severe form of diabetic retinopathy, in which new vessels exhibit abnormal growth. These new vessels grow on the iris and over the drainage angle, causing scar formation and a form of angle-closure glaucoma (Yvonne, 2021).

2.6.1.3 Diabetic Retinopathy:

Mechanism of Development of Retinopathy in Diabetes Mellitus

All forms of diabetes are characterized by hyperglycemia, insulin resistance, relative or absolute lack of insulin action, and the development of diabetes specific pathology in the retina (Centers for Disease Control and Prevention, 2007). Diabetic retinopathy has been one of the major factors of vision impairment in the world. The basic hallmarks of this disease include loss of pericytes, basement membrane thickening, microaneurysms, neovascularization, and blood retinal barrier breakdown (Fong *et al.,* 2003). Molecular and biochemical mechanisms that have been implicated in diabetic retinopathy are increased flux of glucose through the polyol and hexosamine pathways, activation of protein kinase C, and increased advanced glycation end product formation (Brownlee, 2001).

Increased Polyol Pathway Flux

Detrimental effects of hyperglycaemia-induced increase in polyol pathway flux could be explained by a number of proposed mechanisms including decreased (Na^+ and K^+) ATPase activity, sorbitol-induced osmotic stress, decrease in cytosolic NADPH, and increase in cytosolic NADH/NAD^+. The polyol pathway is a two-step metabolic pathway in which glucose is reduced to sorbitol, which is then converted to fructose. Several biochemical and molecular studies implicate the polyol pathway as a reasonable and significant contributor to diabetic retinopathy and other complications of diabetes. Retinal endothelial cells of both rat and human showed aldose reductase immunoreactivity and human retinas exposed to high glucose in organ culture increased the production of sorbitol by a degree comparable to that observed in the rat. Such excess aldose reductase activity can be a mechanism for human diabetic retinopathy (Dagher *et al.*, 2004).

Accumulation of AGEs

It has become established that chronic exposure of the retina to hyperglycemia gives rise to accumulation of advanced glycation end products that play an important role in retinopathy (Zong *et al*., 2011). Advanced glycation end products (AGEs) are proteins or lipids that become nonenzymatically glycated and oxidized after exposure to aldose sugars. Some of the best chemically characterized AGEs in human are carboxyethyllysine (CEL), carboxymethyllysine (CML), and pentosidine, which are shown to play a crucial role in the formation and accumulation of AGE in hyperglycemia. CML and other AGEs have been localized to retinal blood vessels of diabetes patients and were found to correlate with the degree of retinopathy suggesting the pathophysiological role of AGEs in diabetes (Stitt, 2001).

Increased Flux through the Hexosamine Pathway

Hexosamine content has been found to be increased in retinal tissues of humans and rats with diabetes (Okamoto *et al.*, 2001). Recent in vitro and in vivo studies have revealed that the increased flux of glucose via the hexosamine pathway has been implicated in insulin resistance, diabetic vascular complications and stimulation of the synthesis of growth factors (Wang *et al.*, 2012). In particular, it was demonstrated that hyperglycemia-induced production of transforming growth factor-b (TGF-b1), a prosclerotic cytokine, was causally involved in the development of diabetic nephropathy. In the hexosamine pathway, fructose-6-phosphate is converted to N-acetylglucosamine-6-phosphate by glutamine fructose-6-phosphate amidotransferase (GFAT). N-Acetylglucosamine-6-phosphate is then converted to N-acetylglucosamine-1, 6-phosphate, and UDP-GlcNAc. UDP-GlcNAc is a substrate for O-linked glycosylation, which is catalyzed by O-GlcNAc transferase. UDP-GlcNAc, the major product, is the unique donor for the O-linkage of a single N-acetylglucosamine molecule (O-GlcNAc) to many cytoplasmic and nuclear proteins (Giacco and Brownlee, 2010). Glucose is rapidly phosphorylated to glucose-6-phosphate after entering the cell which can then oxidize via glycolysis or the pentose phosphate shunt or stored as glycogen. Before the pathway proceeds, G6P is isomerized to fructose-6-phosphate (F6P) during glycolysis. Fructose-6-phosphate-amidotransferase (GFAT) catalyzes the formation of glucosamine-6-phosphate with glutamine as an amine donor and F6P as an acceptor substrate in the first and rate-limiting step of the pathway. This directly affects retinal microvasculature, caused by prolonged hyperglycemia. It is one of the main diseases causing blindness and visual weakness (Meza *et al.,* 2017). Patients with diabetes often develop ophthalmic complications, such as corneal abnormalities, glaucoma, iris neovascularization, cataracts, and neuropathies. The most common and potentially most blinding of these complications, however, is diabetic retinopathy, (Cai and McGinnis, 2016) which is, in fact, the leading cause of new blindness in persons aged 25-74 years in the United States. Approximately 700,000 persons in the United States have proliferative diabetic retinopathy, with an annual incidence of 65,000. An estimate of the prevalence of diabetic retinopathy in the United States showed a high prevalence of 28.5% among those with diabetes aged 40 years or older (Zhang *et al.*, 2010).

In the initial stages of diabetic retinopathy, patients are generally asymptomatic, but in more advanced stages of the disease patients may experience symptoms that include floaters, distortion, and/or blurred vision. Microaneurysms are the earliest clinical sign of diabetic retinopathy (Bhavsar, 2021).

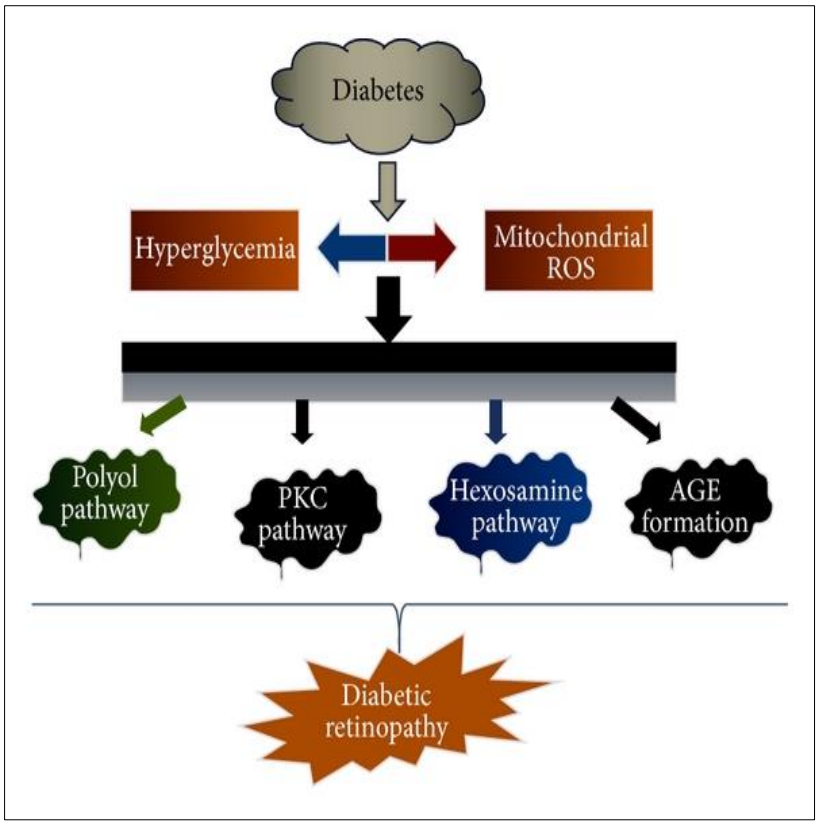

Fig. 4: Mechanism of development of diabetic retinopathy (Safi *et al.*, 2014)

Signs and Symptoms of Diabetic Retinopathy

In the initial stages of diabetic retinopathy, patients are generally asymptomatic; in the more advanced stages of the disease, however, patients may experience symptoms that include floaters, blurred vision, distortion, and progressive visual acuity loss. Signs of diabetic retinopathy include the following:

Microaneurysms:

The earliest clinical sign of diabetic retinopathy; these occur secondary to capillary wall outpouching due to pericyte loss; they appear as small, red dots in the superficial retinal layers.

Dot and Blot Hemorrhages:

Appear similar to microaneurysms if they are small; they occur as microaneurysms rupture in the deeper layers of the retina, such as the inner nuclear and outer plexiform layers.

Flame-Shaped Hemorrhages: Splinter hemorrhages that occur in the more superficial nerve fiber layer.

Retinal Edema and Hard Exudates: Caused by the breakdown of the blood-retina barrier, allowing leakage of serum proteins, lipids, and protein from the vessels.

Cotton-Wool Spots: Nerve fiber layer infarctions from occlusion of precapillary arterioles; they are frequently bordered by microaneurysms and vascular hyperpermeability.

Venous Loops and Venous Beading:

Frequently occur adjacent to areas of nonperfusion; they reflect increasing retinal ischemia, and their occurrence is the most significant predictor of progression to proliferative diabetic retinopathy (PDR).

Intraretinal Microvascular Abnormalities: Remodeled capillary beds without proliferative changes; can usually be found on the borders of the nonperfused retina.

Macular Edema: Leading cause of visual impairment in patients with diabetes (Bhavsar, 2021).

2.6.1.4 Diabetic Nephropathy:

People with diabetes have a higher rate of glomerular filtration, with greater relaxation of the afferent arterioles compared to the efferent ones. It is characterized by increased levels of albumin, hypertension, and reduced glomerular filtration rate (Botas *et al.*,2016).

Diabetic nephropathy is a clinical syndrome characterized by the following (Tang *et al.*, 2016);

A. Persistent albuminuria (>300 mg/d or >200 µg/min) that is confirmed on at least 2 occasions 3-6 months apart
B. Progressive decline in the glomerular filtration rate (GFR)
C. Elevated arterial blood pressure.

Proteinuria was first recognized in diabetes mellitus in the late 18th century. In the 1930s, Kimmelstiel and Wilson described the classic lesions of nodular glomerulosclerosis in diabetes associated with proteinuria and hypertension. By the 1950s, kidney disease was clearly recognized as a common complication of diabetes, with as many as 50% of patients with diabetes of more than 20 years having this complication.

Currently, diabetic nephropathy is the leading cause of chronic kidney disease in the United States and other Western societies. It is also one of the most significant long-term complications in terms of morbidity and mortality for individual patients with diabetes. Diabetes is responsible for 30-40% of all end-stage renal disease (ESRD) cases in the United States. Generally, diabetic nephropathy is considered after a routine urinalysis and screening for microalbuminuria in the setting of diabetes. Patients may have physical findings associated with long-standing diabetes mellitus. Good evidence suggests that early treatment delays or prevents the onset of diabetic nephropathy or diabetic kidney disease. This has consistently been shown in both type 1 and type 2 diabetes mellitus (Bjornstad *et al.*, 2014). Regular outpatient follow-up is key in managing diabetic nephropathy successfully. Recently, attention has been called to atypical presentations of diabetic nephropathy with dissociation of proteinuria from reduced kidney function. Also noted is that microalbuminuria is not always predictive of diabetic nephropathy (Ekinci *et al.,* 2013). Nevertheless, a majority of the cases of diabetic nephropathy present with proteinuria, which progressively gets worse as the disease progresses, and is almost uniformly associated with hypertension.

Aetiology of Diabetic Nephropathy

The exact cause of diabetic nephropathy is unknown, but various postulated mechanisms are hyperglycemia (causing hyperfiltration and renal injury), advanced glycation products, and activation of cytokines. Many investigators now agree that diabetes is an autoimmune disorder, with overlapping pathophysiologies contributing to both type 1 and type 2 diabetes; and recent research highlights the pivotal role of innate immunity (toll-like receptors) and regulatory T-cells (Treg) (Odegaard and Chawla, 2012). Evidence suggests that when there is insulin resistance, the pancreas is forced to increase its insulin output, which stresses the β cells, eventually resulting in β-cell exhaustion. The high blood glucose levels and high levels of saturated fatty acids create an inflammatory medium, resulting in activation of the innate immune system, which results in activation of the nuclear transcription factors-kappa B (NF-κB), and release of inflammatory mediators, including, interleukin (IL)–1β and tumor necrosis factor (TNF)–α, promoting systemic insulin resistance and β-cell damage as a result of autoimmune insulitis. Hyperglycemia and high serum levels of free fatty acids and IL-1 lead to glucotoxicity, lipotoxicity, and IL-1 toxicity, resulting in apoptotic β-cell death.Familial or perhaps even genetic factors also play a role. Certain ethnic groups, particularly African Americans, persons of Hispanic origin, and American Indians, may be particularly disposed to renal disease as a complication of diabetes.

Signs and Symptoms of Diabetic Nephropathy

Diabetic nephropathy should be considered in patients who have diabetes mellitus (DM) and a history of one or more of the following:

- Passing of foamy urine
- Unexplained proteinuria
- Diabetic retinopathy
- Fatigue and foot edema secondary to hypoalbuminemia (if nephrotic syndrome is present)
- Other associated disorders such as peripheral vascular occlusive disease, hypertension, or coronary artery disease.

Pathophysiology of Diabetic nephropathy

Three major histologic changes occur in the glomeruli of persons with diabetic nephropathy. First, mesangial expansion is directly induced by hyperglycemia, perhaps via increased matrix production or glycation of matrix proteins. Second, thickening of the glomerular basement membrane (GBM) occurs. Third, glomerular sclerosis is caused by intraglomerular hypertension (induced by dilatation of the afferent renal artery or from ischemic injury induced by hyaline narrowing of the vessels supplying the glomeruli). These different histologic patterns appear to have similar prognostic significance. The key change in diabetic glomerulopathy is augmentation of extracellular matrix (Batuman, 2021). The earliest morphologic abnormality in diabetic nephropathy is the thickening of the GBM and expansion of the mesangium due to accumulation of extracellular matrix. The image below is a simple schema for the pathogenesis of diabetic nephropathy.

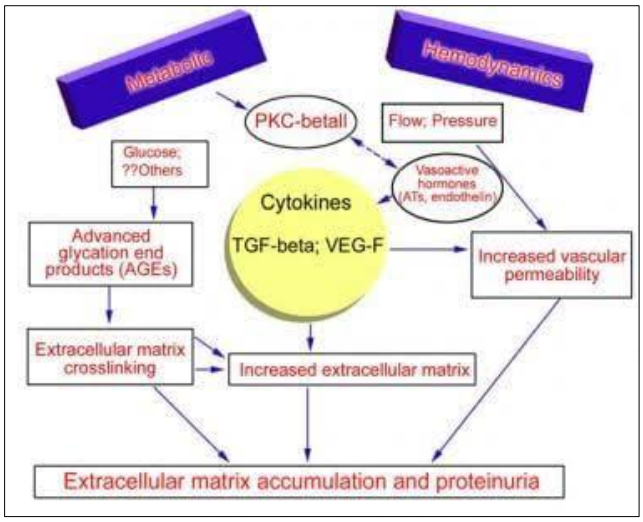

Fig. 5: Simple schema for the pathogenesis of diabetic nephropathy (Batuman, 2021)

Mechanism of Development of Diabetic Nephropathy

The early symptoms in both afferent and efferent glomerulin are glomerular hyperfusion and high filtration, which are the result of decreasing resistance. Afferent arteriole is more robust than efferent arteriole. A variety of causes, such as nitrogen oxide, prostanoids, VEGF, TGF-β1, and the rennin angiotensin mechanism, in particular angiotensin II, have been shown to be implicated in this deficient self-regulatory activity. Early hemodynamic changes limit glomerular capillary leakage and overproduction of the mesangial cell matrix as well as distribution and damage to podocytes of the glomerular basement membrane (Ziyadeh and Wolf, 2008). More mechanical pressure due to these hemodynamic shifts may also contribute to localized release of certain cytokines and growth factors (Wolf and Ziyadeh, 2007). Vasoactive hormone, like angiotensin II and endotheline, mediate changes in renal hemodynamics. The use of renin-angiotensin-blockers preserves kidney activity and anatomy which leads to the production of diabetic nephropathy. Blockage of the renin-angiotensin - aldosterone pathway by raising its TGF-β1 activation antagonizes the profibrotic activity of Angiotensin II (Prabhakar, 2011). The analysis of an animal model of diabetic nephropathy further confirms the idea that diabetic nephropathy underlies such profibrotic effects (Nagai, 2005). Proteinuria and strengthened glomerular structures were decreased by temporary (7 weeks) blockage of the renin-angiotensin network in prediabetic rats. In fact, a regulator of angiotensin-converting enzymes is decreased in TGF-β1 serum rates in patients with type-1 diabetes and nephropathy. Shows there is a link between decreased serum-and-urine TGF-β1 rates and the renewal as defined by glomerular filtration rate shifts.

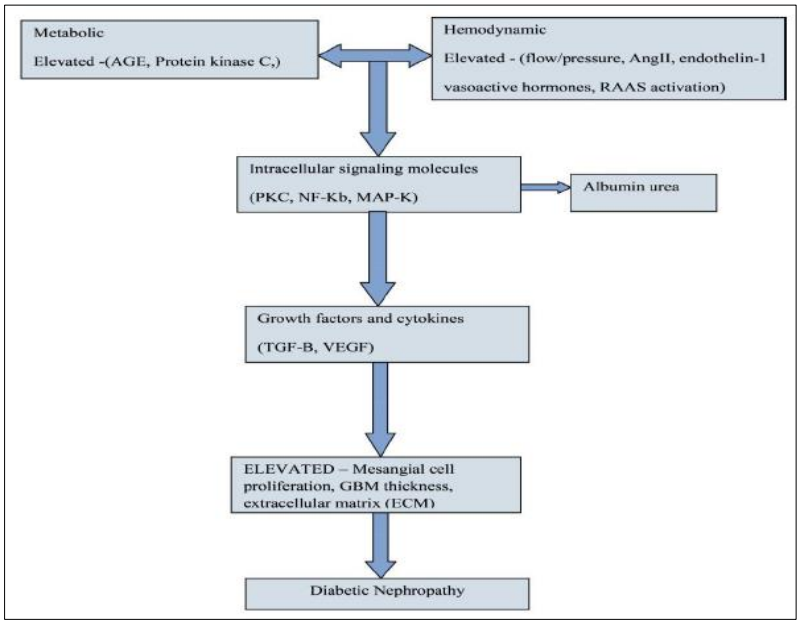

Fig. 6: Mechanism of development of nephropathy (Medha, S. and Bhuvnesh, 2021)

2.6.1.5 Diabetic Neuropathy:

This is a complication that damages the sensory, motor and autonomic fibers of the peripheral nervous system of the lower extremities. The symptoms at the beginning are usually bilateral in the fingers and feet. It may gradually progress to the calf and knee, and acute symptoms and/or paresthesia may be noted in the hands and feet, with deep, burning pain (González *et al.,* 2018). Diabetic neuropathy is the most common complication of diabetes mellitus (DM), affecting as many as 50% of patients with type 1 and type 2 DM. Diabetic peripheral neuropathy involves the presence of symptoms or signs of peripheral nerve dysfunction in people with diabetes after other possible causes have been excluded (Bodman and Varacallo, 2021). In some cases, patients are symptomatic long before routinely performed clinical examination reveals abnormalities. Of all treatments, tight and stable glycemic control is probably the most important for slowing the progression of neuropathy.

Aetiology of Diabetic Neuropathy

Risk factors that are associated with more severe symptoms include the following (Dorsey *et al*., 2009).

- Poor glycemic control
- Advanced age
- Hypertension
- Long duration of DM
- Dyslipidemia
- Smoking
- Heavy alcohol intake
- HLA-DR3/4 phenotype
- Tall height

Pathophysiology of Diabetic Neuropathy

The factors leading to the development of diabetic neuropathy are not understood completely, and multiple hypotheses have been advanced (Zochodne, 2008). It is generally accepted to be a multifactorial process. Development of symptoms depends on many factors, such as total hyperglycemic exposure and other risk factors such as elevated lipids, blood pressure, smoking, increased height, and high exposure to other potentially neurotoxic agents such as ethanol. Genetic factors may also play a role (Tavakkoly-Bazzaz *et al.,* 2010). Important contributing biochemical mechanisms in the development of the more common symmetrical forms of diabetic polyneuropathy likely include the polyol pathway, advanced glycation end products, and oxidative stress.

Mechanism of Development of Diabetic Neuropathy

Polyol Pathway

Increased polyol flux regulated by aldose reductase (AR) activation has been studied most extensively and there is no doubt that this metabolic cascade contributes to the development of neuropathy. Earlier studies proposed the osmotic theory in which increased polyol flux caused intracellular hyperosmolarity by an accumulation of impermeable sorbitol in the cytoplasm, resulting in the expansion of cells and cell lysis. Although this theory might be applied to the genesis of diabetic cataracts, there is no consistent evidence of nerve edema or swollen cells in diabetic nerve tissues. Following the osmotic hypothesis, Greene raised the poor energy utilization theory as the surrogate of osmotic theory. With an accumulation of sorbitol, other osmolytes of myo-inositol, taurine and adenosine were depleted in the cytoplasm. In turn, myo-inositol deficiency caused phosphatidyl-inositol depletion and then poor production of adenosine triphosphate (ATP), leading to reduced Na,K-ATPase activity and protein kinase C (PKC) activity. Indeed, when blood glucose is poorly controlled, severe hyperglycemia can cause neuropathic changes, even in AR-deficient diabetic mice (Yagihashi *et al*., 2008).

Glycation and Advanced Glycation End-Products

Glycation has long been implicated in the pathogenesis of diabetic neuropathy. Every component of nerve tissues can be excessively glycated in diabetic nerves. In fact, deposition of advanced glycation end-products (AGE) was shown in human and animal diabetic nerves, in every component of peripheral nerve tissues (Sugimoto *et al.,* 2008). The deposition was found in the stromal collagens, axoplasms of nerve fibers and Schwann cells, as well as endoneurial vessels. The intensity of AGE deposition detected by carboxymethyllysine immunoreactions correlated well with reduced myelinated nerve fiber density. Hence, AGE was considered to exert injurious processes in the endoneurium through direct toxicity to nerve tissues together with endoneurial microangiopathy.

Oxidative Stress

As a cause of diabetic neuropathy, the generation of free radicals is proposed to be a major factor through increased glycolytic process (Pop-Busui *et al*., 2006). In fact, there are numerous data that showed oxidative stress-induced tissue injury in the peripheral nerve in experimental diabetes (Pop-Busui *et al*., 2006). Based on this background, attempts have been made to inhibit neuropathy with anti-oxidants. In particular, α-lipoic acid has been used for the suppression of oxidative stress in experimental diabetic rats and it was found that it improved NCV delay, nerve blood flow and nerve structure (Stevens *et al.*, 2000). Concurrent with the generation of free radicals during the glycolytic process, mitochondria have a crucial role in cellular death by activation of specific signals and the endonuclease system (Leinninger *et al*., 2006). Hyperglycemia-induced mitochondrial changes include the release of cytochrome C, activation of caspase 3, altered biogenesis and fission, resulting in programmed cell death (Leinninger *et al*., 2006). Excessive entry of glucose causes surplus transport of electrons to generate oxidants in mitochondria, leading to reduced mitochondrial action potentials (MMP) with poor energy synthesis of ATP. Neurotrophic support is also impaired by mitochondrial

damage to cause reduced neurotrophin-3 (NT-3) and nerve growth factor (NGF).

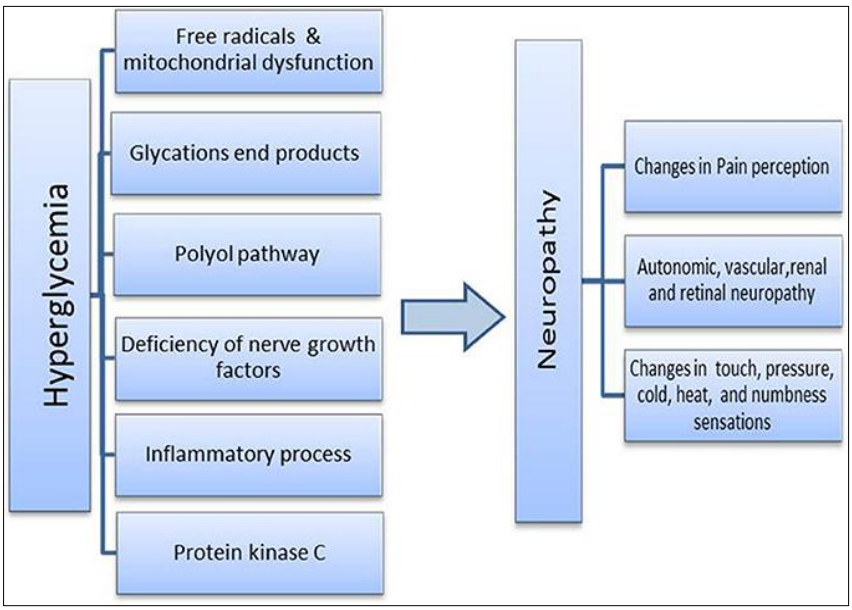

Fig. 7: Mechanism of development of diabetic neuropathy (Alsonousi and Mariff, 2014)

Signs and Symptoms of Diabetic Neuropathy

In type 1 DM, distal polyneuropathy typically becomes symptomatic after many years of chronic prolonged hyperglycemia, whereas in type 2, it may be apparent after only a few years of known poor glycemic control or even at diagnosis.

Symptoms include the following:

- Sensory: Negative or positive, diffuse or focal; usually insidious in onset and showing a stocking-and-glove distribution in the distal extremities
- Motor: Distal, proximal, or more focal weakness, sometimes occurring along with sensory neuropathy (sensorimotor neuropathy)
- Autonomic: Neuropathy that may involve the cardiovascular, gastrointestinal, and genitourinary systems and the sweat glands.

2.6.1.6 Diabetic Foot Ulcer:

The WHO defines it as "the presence of ulceration, infection, and/or gangrene of the foot associated with diabetic neuropathy (ND) and varying degrees of peripheral vascular disease". It is estimated that about 15 to 20% of people with diabetes mellitus may develop an ulcerative lesion throughout their disease. Also, 40 to 60 % of non-traumatic lower-limb amputations occur in diabetics, and 85 % of amputations are preceded by an ulcer (van Battum *et al*., 2011).

Foot ulcers are a common complication of diabetes that is not being managed through methods such as diet, exercise, and insulin treatment. Ulcers are formed as a result of skin tissue breaking down and exposing the layers underneath. They are most common under the big toes and the balls of the feet, and they can affect the feet down to the bones. All people with diabetes can develop foot ulcers, but good foot care can help prevent them (Griffith, 2021). Treatment for diabetic foot ulcers varies depending on their causes.

Symptoms of Diabetic Foot Ulcer

- One of the first signs of a foot ulcer is drainage from the foot that might stain the socks or leak out into shoe. Unusual swelling, irritation, redness, and odors from one or both feet are also common early symptoms.
- The most visible sign of a serious foot ulcer is black tissue (called eschar) surrounding the ulcer. This forms because of an absence of healthy blood flow to the area around the ulcer.
- Partial or complete gangrene, which refers to tissue death due to infections, can appear around the ulcer. In this case, odorous discharge, pain, and numbness can occur (Griffith, 2021).

Causes of Diabetic Foot Ulcers

Ulcers in people with diabetes are most commonly caused by:

- Poor circulation
- High blood sugar (hyperglycemia)
- Nerve damage
- Irritated or wounded feet

Risk Factors for Diabetic Foot Ulcers

All people with diabetes are at risk for foot ulcers, which can have multiple causes. Some factors can increase the risk of foot ulcers, including:

- poorly fitting or poor quality shoes

- poor hygiene (not washing regularly or thoroughly or not drying the feet well after washing)
- improper trimming of toenails
- alcohol consumption
- eye disease from diabetes
- heart disease
- kidney disease
- Obesity (Griffith, 2021).

2.6.2 Macrovascular Complications

The central pathological mechanism in macrovascular disease is the process of atherosclerosis, which leads to a narrowing of the arterial walls throughout the body (Feng *et al*., 2017). They include;

2.6.2.1 Ischemic Heart Disease:

Diabetes mellitus is one the strongest risk factors for cardiovascular disease and, in particular, for ischemic heart disease (IHD). The pathophysiology of myocardial ischemia in diabetic patients is complex and not fully understood: some diabetic patients have mainly coronary stenosis obstructing blood flow to the myocardium; others present with coronary microvascular disease with an absence of plaques in the epicardial vessels. Ion channels acting in the cross-talk between the myocardial energy state and coronary blood flow may play a role in the pathophysiology of IHD in diabetic patients. In particular, some genetic variants for ATP-dependent potassium channels seem to be involved in the determinism of IHD. IHD occurs in the myocardium, which receives insufficient blood and oxygen and an imbalance in the muscle layer. It is divided into: Acute myocardial infarction, which is caused by a thrombus or clot in response to the rupture of an atherosclerotic plaque, which obstructs the blood supply; and, Angina pectoris, which is defined as oppressive chest pain, which are secondary to myocardial ischemia. Apart from the traditional risk factors such as arterial hypertension, dyslipidemia and obesity, hyperglycaemia is an independent risk factor for the development of ischemic heart disease (IHD). Long-term hyperglycaemia leads to vascular damage through several mechanisms. These include oxidative stress, formation of advanced glycation end products, activation of the nuclear factor kappa B and decreased production of nitrogen monoxide (NO). Insulin resistance is believed to have an important bearing on pathogenesis of IHD in type 2 diabetes (DM2) patients (Dresslerová and Vojácek, 2010).

2.6.2.2 Stroke:

This is a rapidly developing clinical syndrome due to a focal disturbance of brain function of vascular origin and lasting more than 24 hours. Peripheral arterial disease (PAD): These are complications affecting arterial, venous and lymphatic vessels that produce a high rate of morbidity and mortality. It is an asymptomatic condition (Fernádez- Miró *et al.,* 2012). Major modifiable risk factors for stroke include hypertension, diabetes, smoking and dyslipidemia. Diabetes is a well-established risk factor for stroke. It can cause pathologic changes in blood vessels at various locations and can lead to stroke if cerebral vessels are directly affected. Additionally, mortality is higher and poststroke outcomes are poorer in patients with stroke with uncontrolled glucose levels (Chen *et al*., 2016).

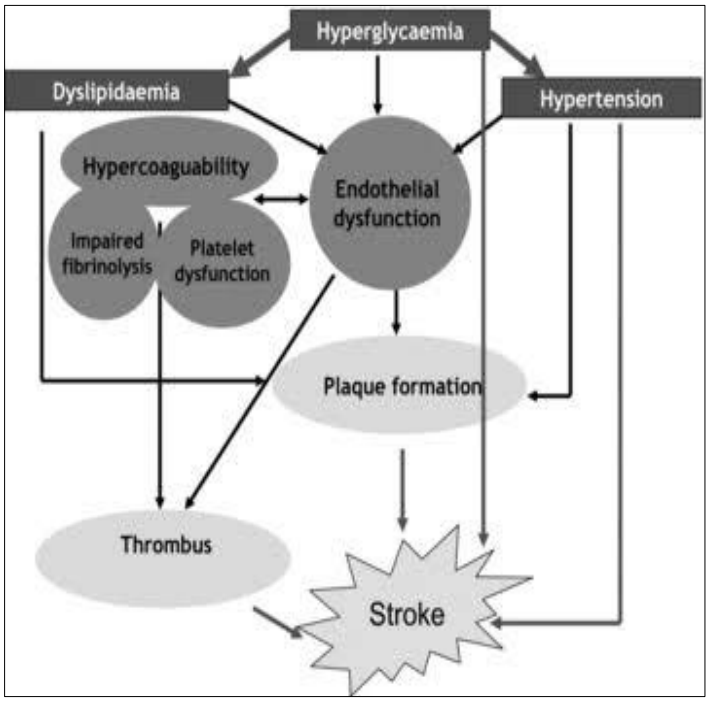

Fig. 8: Development of Stroke in diabetes mellitus (Quinn *et al.,* 2011)

2.7 Factors That Influence Disease Development, Disease Severity/Complications in Type 2 DM

2.7.1 Stress

Increased levels of stress are associated with poor treatment adherence and glycemic control in T2DM patients (Vasanth *et al*., 2017). In a longitudinal study, moderate/high levels of stress were found to be accountable for multifold increase in the incidences of diabetes (Harris *et al*., 2017). Moreover, consistent exposure to stressors, compromised mental health, and psychological stress are highly implicated in increasing risk of T2DM development. Allostatic load (wear and tear in the body occurring as a result of chronic exposure to psychological stress) is assumed to be the major factor responsible for this increased risk of T2DM in such individuals. In addition, consistent stress is also implicated in worsening of clinical outcomes in T2DM patients. Chronic stress is associated with dysregulated glucose metabolism and neuroendocrine function accompanied with low-grade inflammation. A majority of factors that are implicated in T2DM are largely influenced by psychological stress including the release of glucose (and lipids) in circulation, expression of inflammatory cytokines, and elevated blood pressure (Hackett and Steptoe, 2017). In one study, in type 2 diabetes patients when exposed to acute stress during the postprandial period, considerable increases in blood glucose levels were observed. Apparently, treatment strategies, including stress management interventions, are a promising approach in effectively preventing or controlling the incidence of type 2 diabetes.

2.7.2 Irregular Sleep Pattern

Although physical activity and maintained dietary pattern result in considerable improvements in the management of T2DM, they cannot be envisioned as the sole contributors to the worsening of diabetes incidences. Sleep is another modifiable lifestyle behavior that has proven roles in influencing metabolic health and energy status. Optimization of sleeping patterns is crucial in diabetes control (Arora and Taheri, 2015). A population-based study suggests that short sleep (<5 h) or insomnia is associated with increased risk of T2DM. In similar studies, poor sleep was associated with higher HbA1c levels (>7%) and insulin resistance in T2DM patients [88]. Disturbed circadian rhythms and sleep-wake patterns also result in significant effect on onset, development, and management of diabetes (Arora and Taheri, 2015). Shift workers tend to remain much prone to metabolic disorders due to consistent sleep loss and disrupted circadian rhythm.

In addition, developed propensity of napping as a consequence of poor or insufficient nocturnal sleep is also associated with high risk of T2DM. In one study, experimental manipulation of sleep and circadian pattern resulted in significant reduction in insulin response to standardized meal which could be recovered with restored sleeping patterns (Buxton *et al.*, 2012). Changes in hormones that regulate appetite (leptin and ghrelin) are observed to be associated with short sleep causing an increased urge for carbohydrate-rich food and increased calorie intake (Arora and Taheri, 2015). Moreover, lack of sleep also results in oxidative stress and release of orexin or hypocretin, a neuropeptide that regulates sleep and appetite and causes the stimulation of sympathetic nervous system and increased release of cortisol with simultaneous decrease in growth hormone secretion, all leading to considerable hyperglycemia (Arora and Taheri, 2015).

2.8 Role of Oxidative Stress in Type 2 Diabetes Mellitus

Reactive oxygen species (ROS) are chemically active oxygen-containing molecules generated in living systems. They are oxygen metabolism natural by-products in all aerobic organisms (Oxidative Stress, 2020). The main ROS types include superoxide, hydroperoxyl radical, singlet radical, hydroxyl radical, nitric oxide, peroxynitrite, etc (Sies and Jones, 2020). ROS are primarily generated in mitochondria, but there are also alternative mechanisms that contribute to their formation: NADPH-oxidase (NOX), immune reactions, xanthine oxidase, arachidonic acid metabolism, etc (Forrester *et al*., 2018). ROS are widely involved in the processes of intracellular signaling and regulation of cell activity, apoptosis induction, adaptation to the effects of various factors, and immune response (Sies, 2020). Moreover, ROS can stimulate inflammatory responses through protein kinases, transcription factors, and proinflammatory factors genomic expression (Mehta *et al.,* 2017; Ehiaghe *et al*., 2025a; Ehiaghe *et al*., 2025b). Increased ROS accumulation leads to oxidative stress (OS), which contributes to major cellular components damage, including lipids, proteins, and DNA (Sifuentes-Franco *et al*., 2017). The antioxidant defense (AOD) system provides critical defense for the biological system by limiting the damaging effects of ROS. There are many antioxidant enzymes, including superoxide dismutase (SOD), glutathione peroxidase (GPx), glutathione reductase (GR), catalase, paraoxanase (PON), etc (Ozougwu, 2016). In addition to enzymatic antioxidants, non-enzymatic antioxidant defense (ascorbate, tocopherols, retinol, carotenoids, reduced glutathione (GSH), melatonin, polyphenols, ceruloplasmin, carnosine, etc.) also plays an important role in maintaining normal ROS levels (Mirończuk-Chodakowska *et al*., 2018). Under different pathological conditions, including DM, the redox balance can be disturbed that leads to negative consequences for the cell (Oxidative Stress, 2020).

2.8.1 Molecular Mechanisms of Oxidative Stress (OS) Development in DM

At present, there is strong evidence of direct involvement of hyperglycemia in the initiation of vascular complications of DM, while OS associated with enhanced ROS generation plays a crucial role in their pathogenesis (Bigagli and Lodovici, 2019). The main molecular mechanisms associated with OS in DM have

been determined and they are associated with glucose and lipid metabolism (Ighodaro, 2018). Thus, several metabolic pathways that stimulate OS development under glycemic conditions are considered: glycolytic pathway, enhanced formation of advanced glycation end products (AGE), hexosamine pathway, activation of protein kinase C (PKC), polyol pathway, and deactivation of the insulin signaling pathway (Chernikov *et al.,* 2017). Under hyperglycemia conditions, excessive production of ROS during glycolysis reactions is observed. It leads to DNA damage and subsequent activation of poly-ADP-ribose polymerase 1 (PARP1), a DNA repair enzyme (Rolo *et al*., 2006). PARP1 inhibits glyceraldehyde-3-phosphate dehydrogenase (GA3PDG) activity, which leads to accumulation of glyceraldehyde-3-phosphate (GA3P) and other glycolysis intermediates, such as fructose-6-phosphate (F6P) and glucose-6-phosphate (G6P) (Giacco and Brownlee, 2010). The increase in the content of GA3P activates other prooxidant pathways, including polyol, hexosamine pathways, etc. (Rolo and Palmeira, 2006). In addition, GA3P accumulation can cause glucose autoxidation, which leads to the hydrogen peroxide formation that contributes to OS. Glucose autoxidation can occur due to its accumulation in cells. This leads usually to the formation of glyoxal, an AGE precursor, and definitely promotes cellular OS (Dariya and Nagaraju, 2020).

2.8.1.1 Formation of AGE-Products (Carbonyl Stress)

Under hyperglycemia conditions, glucose autoxidation occurs and carbonyl compound glyoxal, an AGE-precursor is forming. Also, glucose metabolites, such as GA3P and dihydroxyacetone-3-phosphate, non-enzymatic dephosphorylation gives methylglyoxal, another precursor of AGE. Glyoxal and methylglyoxal bind to different receptors of AGE (AGE-R1, AGE-R2, AGER3 and receptor for advanced glycation end products) or interact with different biomolecules, causing OS directly or indirectly through PKC activation (Asadipooya and Uy, 2019). 3-Deoxyglucosone is the third precursor of AGE, it is formed by the cleavage of the glucose-derived adduct of lysine 1-amino-1-deoxyfructose, commonly referred to as the Amadori product (Maleki *et al.,* 2020). It was found that other extracellular matrix components, lipids and nucleic acids, can also be converted into AGE (Lotfy *et al.*, 2017). Modern concept of OS provides its relationship with carbonyl stress, as a result of which an active synthesis of carbonyl compounds occurs. This relationship is evident also for DM.

2.8.1.2 Hexosamine Pathway of Glucose Oxidation

Under glycemia conditions, the F6P level increases and the molecule is metabolized by glucosamine-fructose aminotransferase to glucosamine-6-phosphate, which subsequently turns into uridine phosphate-N-acetylglucosamine (UDP-GlcNAc) through activity of UDPN-acetylglucosamine-1-phosphate uridyltransferase. Accumulation of UDP-GlcNAc triggers activation of O-glucosamine-N-acetyltransferase, which is associated with the prooxidant role of the hexosamine pathway in DM. Activity of this enzyme and hexosamine pathway is associated with changes in gene expression and increased expression of transcription factors TGF-α and TGF-β that inhibit mitogenesis of mesangial cells, activate the proliferation of the collagen matrix and thickening of the basement membrane (Daniels *et al*., 2020).

2.8.1.3 PKC Activation Pathway

PARP1 that is activated as a result of DNA damage caused by OS, inhibits GA3PDG activity, which leads to GA3P and its isomer, dihydroxyacetone-3-phosphate (DHA3P) accumulation. DHA3P, which in the presence of free fatty acids, is oxidized to glycerol-3-phosphate by the glycerol-3-phosphate dehydrogenase, forms diacylglycerol, which interacts with the AGE receptor, stimulating OS reactions through PKC activation (Ighodaro, 2018).

2.8.1.4 Polyol Pathway of Glucose Oxidation

In hyperglycemia, aldose reductase is activated that leads to an increase in the level of sorbitol that is converted by sorbitol dehydrogenase to fructose. High levels of fructose cause accumulation of GA3P and DHAP that leads to OS due to methylglyoxal formation and PKC activation (Giacco and Brownlee, 2010). In addition, increased activity of aldose reductase causes a decrease in NADPH levels, which subsequently leads to GPx activity and glutathione levels decrease. This situation causes the AOD suppression, which leads to OS.

2.8.1.5 Deactivation of the Insulin Signaling Pathway

Hyperglycemia leads to activation of uncoupling protein-2 (UCP-2), which results in a decrease in ATP/ ADP ratio and inhibition of the ATP-dependent pathways leading to secretion, release, and action insulin (Holley *et al.*, 2015). OS causes deactivation of the main signaling pathways that are usually activated during the action of insulin (Cb1, PI3K, and p38 MARK) by stimulating activity of phosphatases such as protein tyrosine phosphatase 1B and SH2-containing tyrosine protein phosphatase, resulting in termination of insulin action (Langlais *et al*., 2011). OS also activates several stress-sensitive signaling pathways that contain components such as NF-κB, inflammatory molecules such as inducible NO synthase, and a class II histocompatibility complex (Asmat *et al.*, 2016). These processes greatly and generally contribute to impairment of insulin secretion and action. Oxidative damage to β-cells caused by ROS as a result of hyperglycemia affects the quantity and quality of secreted insulin (Saeedi *et al.*, 2019). There are data that β-cell dysfunction (impaired secretory ability and increased insulin resistance) caused by OS plays an important role in the DM1 and DM2pathogenesis (Ceriello *et al*., 2016). Excessive ROS production in β-cells can cause changes in the shape,

volume, and function of mitochondria, which contributes to disintegration of ATP-dependent K+channels and impaired insulin secretion (Chandra *et al.,* 2019). These processes can be due to the fact that the content of antioxidant enzymes in β-cells is 10-20-fold lower than in cells of the liver, kidneys, heart, brain, and other organs (Tavakoli *et al*., 2017). It was found that the expression of mitochondrial Mn-dependent SOD2 and cytoplasmic Cu/Zn-dependent SOD1 genes does not exceed 50% of the level of their synthesis in the liver, the content of GPx and catalase is 5% (Tavakoli *et al*., 2017). As a result, islet cells are most sensitive to the attack of ROS and other diabetogenic agents. Nitric oxide (NO), an unstable radical whose oxidation products are nitrates and nitrites, also takes an active part in the destruction and death of β-cells mechanisms (Ceriello *et al.*, 2016). NO, cytokines, and other forms of ROS can affect the process of genetically programmed cell death, apoptosis, which is based on the endonuclease activation leading to fragmentation of genetic material and death of β-cells (Lofty *et al*., 2017). OS in relation to DM can play a dual role, contributing not only to its manifestation, but also to escalation of the disease and related complications. ROS can activate several other pathways, which, in turn, cause one of the main complications of DM endothelial dysfunction (Ceriello *et al.,* 2016). Endothelial dysfunction is an independent risk factor for cardiovascular complications of DM, contributes to the leukocytes and platelets adhesion, thrombosis and inflammatory reactions development, which are the most important factors of atherosclerosis (Pickering *et al.*, 2018). It was found that even short-term exposure to hyperglycemia leads to a selective increase in the expression of iNOS gene, followed by an increase in NO. Simultaneous elevation of NO and superoxide radicals increases the formation of peroxynitrite, which is a strong oxidant with a toxic effect on the vascular network, which can contribute to the disease progression and myocardium damage (Ghasemi-Dehnoo *et al.*, 2020). Various isoforms of NOX are expressed in monocytes, macrophages, and vascular cells, and both perform a protective role and contribute to the development of endothelial dysfunction and inflammation. Activation of PKC, AP-2 and AGE generation, increase the expression of NOX isoforms in monocytes and macrophages, stimulate ROS increase, as well as the synthesis of proinflammatory proteins such as IL-6, monocyte chemoattractant protein 1(MCP-1), and intercellular adhesion molecules 1 (ICAM-1) (Kanikarla-Marie and Jain, 2015). OS plays a major role in progression of other serious complications of DM: neuropathy, nephropathy, and retinopathy. The main ROS sources in the kidneys are NOX enzymes, in particular NOX4 and NOX5 homologues. Various factors affect the expression and activity of these enzymes, which leads to the proinflammatory and profibrotic markers growth, including NF-κB p65 subunit, TNFα, TGF-β, and fibronectin (Holley *et al.,* 2015). At the molecular level, the initial driver of diabetic retinopathy is glucose, which affects the same metabolic pathways, including the polyol, hexosamine pathway, PKC, and the AGE/RAGE axis. In endothelial cells of retinal microvessels, OS leads to a decrease in the expression of hypoxia-induced factor alpha (HIF1α), which, in turn, activates vascular endothelial growth factor (VEGF), which stimulates angiogenesis (Kang and Yang, 2020). OS increases retinal inflammation by increasing the expression of proinflammatory proteins (NF-κB-factor, MCP-1, and ICAM-1). In addition, Müller cells promote OS-induced inflammation by glial fibrillar protein activation (GFAP) (Pickering *et al.,* 2018). In diabetic neuropathy, OS induced by hyperglycemia stimulates damage to nerve cell through LPO, DNA damage, with pathological activation of repair pathways, exhaustion of cell antioxidants, and induction of proinflammatory transcription factors. High intensity of free processes promotes the expression of redox-sensitive genes of AOD enzymes. Their promoters have binding sites with transcription factors — NF-κB, AP-1, Nrf2, FoxO, PPARS, and Bach 1, NF-κB/ARE system, regulating the development of inflammation and AOD activity. Insulin is involved in the regulation of antioxidant enzyme activity through the expression of Nrf2 and NF-κB transcription factors by insulin-dependent effector proteins (Akt kinase, MARK) (Wang *et al.*, 2012). Currently, OS reactions associated with hyperglycemia in DM are considered in the context of the "metabolic memory phenomenon, when the modification of biomolecules by ROS can lead to cellular dysfunctions a long time later after of DM manifestation. Thus, newly identified DM1 and DM2 large epidemiological studies showed that early and intensive interventions aimed at stabilizing hyperglycemia and risk factors associated with cardiovascular diseases prevent the onset and slow the progression of late chronic complications (Ceriello *et al.*, 2016). However, despite the improvement of DM control in the later period, hyperglycemia in the early stages necessarily leads to these specific complications onset and progression, even after 30 years. It was demonstrated that AGEs and their receptors are involved in the metabolic memory formation by NF-κB factor activation, which increases the expression of genes responsible for vascular damage. OS also determines epigenetic changes, such as chromatin modification (including histone modification) and DNA methylation. These changes allow cells to quickly adapt to environment changes, are remembered even in conditions of normoglycemia, and are passed on to the next generation (Kowluru, 2013).

2.9 Antioxidant Status in Type 2 Diabetes Mellitus

2.9.1 Total Antioxidant Capacity (TAC)

Oxidative stress is considered as another factor resulting in increased risk of type 2 DM by means of cytotoxicity in pancreatic beta cells, insufficient insulin production or action, and endothelial dysfunction (Gerber and Rutter, 2017).

Antioxidants show a defensive role in the progression of type 2 DM by reduction of oxidative

stress via glucose oxidation reaction, non-enzymatic glycation of proteins, and lipid peroxidation (Thakur and Kumar, 2018; Ogbodo *et al*., 2019). Total antioxidant capacity is a parameter to estimate the status of all antioxidants present in plasma/serum and other body fluids (Rubio *et al*., 2016). TAC also provides overall information regarding the capacity of reactive oxygen species (ROS) (Manafa *et al*., 2017). ROS cause oxidation damage in tissue. It causes hindrance in the metabolic mechanism of macromolecules (lipids, carbohydrates, and proteins etc.) and cause non-communicable diseases such as type 2 DM, CVD, obesity, hypertension, neurodegenerative diseases and cancer. In human beings, a highly complex antioxidant system developed in various biological fluids, which depends upon the enzymatic and non-enzymatic antioxidants including glutathione peroxidase, superoxide dismutase, glutathione and uric acid that perform different functions interchangeably and sometimes symbiotically to neutralize the effect of free radicals and protect body from free radical toxicity (Asmat *et al.*, 2016). Under normal circumstances, a critical balance is maintained between oxygen free radicals and antioxidant defence systems. Impairment in the equilibrium of oxidant and antioxidant gives rise to oxidative stress, resulting in type 2 DM and CVD (Pieme *et al.,* 2017). Intake of antioxidant supplements such as ascorbic acid, tocopherols, and cerotenoids reduce the effect of ROS and prevent type 2 diabetes mellitus and its complications like nephropathy, retinopathy, and CVD. Various studies suggested that dietary supplements of antioxidants along with usual food consumption decrease the morbidity and mortality rate (Ashadevi and Gotmare, 2015).

A study by Jabeen *et al.,* (2018) and Onah *et al*., (2013) suggests that decrease levels of antioxidant status increase lipid peroxidation which may cause oxidative stress in type 2 DM. Furthermore, high levels of BMI, SBP, DBP, FBS, TC, TG, LDL- C and low levels of HDL-C may also enhance the progression of oxidative stress in type 2 DM subjects which promotes the development of obesity, CVD, hypertension, and other metabolic diseases (Ogbodo *et al*., 2023). In type 2 diabetic subjects, oxidative stress is prevented by dietary modifications and healthy lifestyle by means of scavenges of ROS. Dietary antioxidants along with early interventions improve the durability and quality of life of type 2 diabetic subjects.

2.9.2 Total Oxidant Capacity (TOC)

Oxidative stress occurs in response to the oxidative damage caused when the body's antioxidative and scavenging activities cannot cope with the active oxidants produced by a harmful stimulant. Oxidative stress involves macromolecular oxidative damage, induces tissue protein denaturation, DNA damage, and lipid peroxidation, and interferes with the body's normal metabolic activity, leading to the occurrence and/or development of diseases. It has been confirmed that oxidative stress is involved in a variety of diseases, such as pneumonia, pancreatitis, diabetic nephropathy (Nam *et al.*, 2009), cardiovascular disease, nervous system disease and cancer. Reactive oxygen species (ROS) make up the majority of active oxides, and account for more than 95% of total oxides.

2.10 Traditional Methods of Managing Complications in type 2 DM

The prevalence of diabetes mellitus is constantly increasing, making this disease a global health problem. Efficient diabetes management is necessary in order to decrease the risk of both micro-and macrovascular complications such as cardiovascular diseases or diabetic nephropathy (Zheng *et al*., 2018) especially when patients are also diagnosed with other comorbidities such as hypertension or depression (Khan *et al.*, 2018).

The most commonly used oral medications for treatment of type 2 diabetes include:
Metformin: This reduces insulin resistance and allows the body to use its own insulin more effectively. It is regarded as the first-line treatment for type 2 diabetes in most guidelines around the world.
Sulfonylureas: They stimulate the pancreas to increase insulin production. Sulfonylureas include gliclazide, glipizide, glimepiride, tolbutamide and glibenclamide

Management of Diabetic Nephropathy

Several issues are key in the medical care of patients with diabetic nephropathy (Burney *et al*., 2009). These include glycemic control, management of hypertension, and reducing dietary salt intake and phosphorus and potassium restriction in advanced cases.

Agents for glycemic control in patients with diabetes who have kidney disease include the following:

i. Dipeptidyl peptidase inhibitors
ii. Alpha-glucosidase inhibitors
iii. Sodium-glucose cotransporter 2 (SGLT2) inhibitors
iv. Glucagonlike peptide-1 (GLP-1) receptor agonists or incretin mimetics
v. Amylin analogs
vi. Nonsteroidal, selective mineralocorticoid receptor (MR) antagonists.

2.11 Current Advances in the Diagnosis of Complications Associated with Type 2 DM

2.11.1 Diagnosis of Diabetic Retinopathy

Some of the biomarkers that can be utilized in the diagnosis of retinopathy include;

Vascular Endothelial Growth Factor (VEGF)

VEGF is currently implicated as a mediator of NPDR and an initiator of PDR. VEGF has been widely studied and is postulated to have multiple roles in the pathogenesis of DR making it a logical target as a marker and the work done so far seems to support its potential in

this light. A positive correlation between serum levels of VEGF and the incidence of DR (Ozturk *et al*., 2009) with the VEGF levels correlating with the stage of retinopathy (Cavusoglu *et al*., 2007) have been demonstrated. A cross sectional analysis of 69 diabetic patients (30 NDR, 23 NPDR, and 16 PDR), were able to show an increasing serum VEGF trend with increasing severity of DR, with a statistically significant difference between NDR vs. NPDR ($p = 0.007$) which would suggest it does have potential as a screening marker (Du *et al.*, 2014).

MicroRNA (miRNA)

miRNAs are a class of highly conserved 1925 nucleotide noncoding RNAs that regulate gene expression at the posttranscriptional level. By annealing to partially complementary sequences in the target mRNAs, miRNAs mediate translational repression or degradation of mRNAs, resulting in the downregulation of protein expression (Wu *et al*., 2012). There is evidence that several miRNAs target specific mRNAs for regulating the progression of DR. These include miRNAs-126, -200b, and -31, all of which are involved in vasculature regulation and therefore are crucial for suppressing angiogenesis in DR. miRNAs-146, -155, -132, and -21 have role in the chronic inflammation that is a key factor in the development of DR (Xiong *et al.*, 2014). Other miRNAs whose level has been shown to be altered in patients with DR but whose role remains to be clearly defined include miR-182, -96, -183, -211, -204, and -124 which were significantly increased during progress of DR, and miR-10b, -10a, 219-2-3p, -144, -338, -199a-3p which were significantly decreased (Wu *et al.*, 2012). Others with altered levels include miR-24, -323, -92a, -369, -219, -203a,-34c, -350, -410, -592, -758, -216a, -351, -137, -935 (upregulated), and miR-375 and -212 which are downregulated (Xiong *et al.,* 2014).

Chemerin

Serum levels of chemerin, a multifunctional peptide involved in lipid and glucose metabolism (Fatima *et al*., 2015) has also been found to be elevated in patients with NPDR and PDR (Du *et al.*, 2016). This study analyzed 60 T2DM patients (15 with PDR, 20 with NPDR, and 25 with no DR) and 20 healthy controls. Among the diabetic patients the serum chemerin levels were demonstrated to increase with increasingly severe eye disease; the difference in chemerin was statistically significant ($p < 0.05$) between the three groups. A trend chi-square showed that the chemerin level was correlated with the severity of DR ($\chi 2 = 16.07$, $p < 0.001$). In addition, levels of chemerin were also found to correlate positively with levels of other markers associated with markers of obesity, inflammation, and neovascularization namely CRP and VEGF.

Apelin-13

Apelin-13, a ligand of G-protein coupled receptor which has been shown to be involved in retinal angiogenesis was also targeted as a potential biomarker (Du *et al*., 2014). This study recruited 69 type 2 diabetics, 16 with PDR, 23 with NPDR, and 30 with NDR. Serum levels of apelin-13 were significantly elevated in the PDR group compared to the no DR group ($p = 0.041$).

Advanced Glycation End-Products (AGEs)

AGEs especially carboxymethyllysine (CML) has been demonstrated to be elevated in the serum of patients with diabetic retinopathy (Mishra *et al*., 2015). Significant differences were found in serum levels of N-epsilon carboxymethyl lysine between healthy controls and diabetics both with and without eye disease as well as increasing with progressive severity of DR.

Pentosidine

This has also been the focus of several studies, often in combination with CML. While it has been demonstrated to be increased in the serum of patients with DR, overall it appears less sensitive than CML in detection of DR (Kerkeni *et al.*, 2012).

Imaging studies used in the diagnosis of diabetic retinopathy include the following:

Fluorescein Retinal Angiography:

Microaneurysms appear as pinpoint, hyperfluorescent lesions in early phases of the angiogram and typically leak in the later phases of the test. This method is similar to retinography, but the contrast agent fluorescein is injected into a vein. When this dye reaches the fundus of the eye it highlights any changes in retinal blood flow and, chiefly, the presence of neovascularisation and haemorrhages. This test cannot be performed on people with a fluorescein allergy and must be conducted with special care in patients with kidney problems. Patients who undergo this test may produce yellow urine for the next 24 hours.

Optical Coherence Tomography Scanning:

Administered to determine the thickness of the retina and the presence of swelling within the retina, as well as vitreomacular traction. This technique uses a light beam to scan the inner retina (macula). It produces cross-sectional images of the different layers in the retina. It is particularly useful for examining diabetic macular oedema.

Optical Coherence Tomography Angiography

A novel imaging technique, known as optical coherence tomography angiography, has recently been developed for examining patients with abnormal retinal blood circulation. Over the last 10 years, optical coherence tomography has revolutionised the field of ophthalmology, since it provides highly detailed images of the retina's anatomy and without any side effects. Nevertheless, until recently, it only produced information about tissues rather than blood vessels, which could be used to diagnose and monitor accumulations of fluid in the macula (diabetic macular oedema). Building on this technique, new computer processing technology means we can now obtain images of the retinal circulation (angiography). Therefore,

ophthalmologists now capture images like those produced by traditional fluorescein angiography but without having to inject a dye that can cause side effects. With this test, patients can undergo detailed examinations on a regular basis and without additional risks. The new information gathered by this technique is very important in a lot of fields researching the disease (BBVA Foundation, 2018)

B-Scan Ultrasonography

Binocular Indirect Ophthalmoscopy (BIO)

Ophthalmoscopy with or without the pupil dilated is the standard procedure in the screening for diabetic retinopathy (DR), in which detection of microaneurysms in the posterior pole is the earliest clinical sign (Wiley and Ferris, 2013). Fluorescein angiography is an invasive, costly, and time-consuming technique but is a sensitive method to detect vascular changes due to rupture of the inner and outer blood retinal barrier in the course of an established DR. In contrast to retinography or fluorescein angiograms, OCT provides high-resolution images of the retinal layers, choroid, vitreous gel, and the vitreoretinal interface and has become the gold standard for the diagnosis, treatment approach, prognosis, assessment of treatment response, and control of patients with DME. Because of the advantages of the speed and ease of image acquisition as compared to other examinations, the association of OCT to retinography may increase the sensitivity of early diagnosis/screening in the diabetic patient.

Optical Coherence Tomography Angiography (OCTA)

OCT angiography (OCTA) is a new non-invasive imaging technique that employs motion contrast imaging to high-resolution volumetric blood flow information generating images similar to angiographic images in a matter of seconds (de Carlo *et al*., 2015). It provides a highly detailed view of the retinal vasculature, which allows for accurate delineation of the foveal avascular zone (FAZ) and detection of subtle microvascular abnormalities, including FAZ enlargement, areas of capillary nonperfusion, and intraretinal cystic spaces (Spaide *et al*., 2015). The possibility of detecting microvascular changes in diabetic eyes before the presence of visible microaneurysms may have important implications in the future. As OCTA is fast and noninvasive, it can provide a sensitive method for detecting early changes in DR, constituting a very promising technique for early diagnosis and control of treatment in patients with DR (Ishibazawa *et al.*, 2015). In this sense, OCTA could be able to quickly identify diabetic individuals at risk for developing retinopathy, which in turn would require more frequent examinations and a higher optimization of metabolic control.

2.11.2 Diagnosis of Diabetic Neuropathy

Diabetic neuropathy is the earliest and most frequent complication of the three major complications associated with diabetes, but it is often not diagnosed until the disease has seriously progressed (Feldman *et al.,* 2019). Therefore, early diagnosis is extremely important for care and treatment. This complication is peripheral neuropathy with predominant sensory impairment, and its symptoms are hyperesthesia, pain, and a gradual loss of sensation due to the loss of nerve fibers. When hypoalgesia occurs, trauma and mechanical irritation cannot be noticed; as a result, foot ulcers and gangrene may occur, leading to amputation of the lower limbs (Pop-Busui *et al*., 2017). Therefore, since this disease imposes a physical and mental burden on patients and their families and decreases the quality of life, it is important to develop diagnostic methods with high sensitivity for its early detection. It has been clarified that the onset and progression of neuropathy can be suppressed by strictly controlling the blood glucose levels of diabetic patients over long periods of time (Martin *et al*., 2006) however, it is difficult to completely prevent neuropathy. Currently, symptomatic treatment is the only option, as there is no reliable and effective treatment method. It has been reported that up to 50% of diabetic peripheral neuropathy cases can be asymptomatic (Galer *et al.,* 2000). Therefore, together with clinical symptoms and neurological findings for the early detection of diabetic neuropathy, more sensitive and convenient biomarkers that detect the severity or stage progression are required.

Biomarkers for Diabetic Neuropathy

Biomarkers for diabetic neuropathy are divided into four groups:

a) AGE-related molecules (methyl glyoxal and glyoxalase I),
b) Molecules that participate in the progression of inflammation (Toll-like receptors, TNF-α, miR-146a, adiponectin, etc.),
c) Molecules associated with nerve damage (nerve specificity enolase and semaphorin), and
d) Molecules involved in nerve protection (nerve growth factor and HSP27).

Group (a) is considered the causative agent of the onset of diabetic neuropathy, and the biomarkers from groups (b)–(d) are regarded as those that manifest in the late stage of disease progression.

AGEs and Their Precursors

Non-enzymatic glycation of proteins has been established as a major cause of diabetic complications, such as nephropathy and macroangiopathy. Excessive accumulation of AGEs is also observed in peripheral nerve tissue in diabetic neuropathy, which has been shown to correlate with a decrease in the number of nerve fibers. Impaired axonal transport due to the modification of major axonal cytoskeletal proteins, such as tubulin, by AGEs (Sugimoto *et al*., 2008) and impaired axon regeneration due to modification of the basement membrane protein laminin (Duran-Jimenez *et al.*, 2009) are thought to contribute to the development of neural

lesions. In addition, in knockout mice lacking AGE receptors (AGEs: RAGE), the loss of pain perception was prevented, demonstrating that RAGE expression is directly involved in the onset of neuropathy (Bierhaus *et al.,* 2004). Accumulation of AGEs in nerve tissue is considered to be a major cause of the onset and progression of neuropathy in humans. However, the measurement of AGEs in tissues is difficult in terms of the collection and quantification of samples and does not seem to be suitable as a biomarker. On the other hand, reactive dicarbonyls, such as methylglyoxal and α-oxoaldehyde which are precursors of AGEs, are receiving much attention as biomarkers for predicting the onset and progression of diabetic neuropathy (Thornalley, 2002). Bierhaus *et al*. (2012) reported that methylglyoxal depolarizes sensory nerves, causes post-translational modification of the voltage-gated sodium channel Nav 1.8, and induces hyperalgesia. Furthermore, it was reported that the cold receptor channel transient receptor potential cation channel A1 (TRPA1) was also activated, causing temperature and mechanical hyperalgesia (Anderson *et al.*, 2013). When methylglyoxal was administered to mice, a decrease in nerve conduction velocity and promotion of the secretion of calcitonin gene-related peptides from cutaneous nerve endings were observed, and hyperalgesia to heat stimulation and mechanical stimulation was induced. Similar changes were observed in streptozotocin-induced and hereditary diabetic mouse models but not in Nav 1.8 knockout mice. Likewise, microinjection of methylglyoxal into the skin of healthy human volunteers also induces chemical pain sensations and thermal hyperalgesia (Düll *et al.,* 2019). These findings strongly suggest that the mechanism of hyperalgesia in diabetic neuropathy is due to methylglyoxal itself. Furthermore, recent reports from animal experiments have shown that both hyperalgesia and itching and hypoalgesia are induced by direct intradermal or intrathecal injection (Cheng *et al.,* 2019). Therefore, methylglyoxal can reproduce various symptoms of diabetic neuropathy that resemble clinical symptoms. Hansen et al. reported no association between serum methylglyoxal and the occurrence of diabetic peripheral neuropathy in a cohort of well-treated patients with short-term type 2 diabetes (Hansen *et al*., 2015). On the other hand, Andersen *et al*. (2018) reported a significant association, suggesting that higher levels of methylglyoxal are identified as risk factors for the development of diabetic neuropathy.

Glyoxalase I (GLOI)

It is well known that there is a pathway for degrading reactive dicarbonyls such as methylglyoxal in vivo by glyoxalase I (GLO I), the rate-determining enzyme (Thornalley, 2003). Recently, it has been shown that the expression of GLO I varies in sensory neurons from two inbred strains of mice. Neuropathic symptoms, such as a decreased pain threshold and decreased intraepidermal nerve fiber density, observed in diabetic conditions are significantly suppressed in mice with high GLO I activity (Jack *et al.,* 2012). From these results, it can be assumed that the presence or absence of GLO I gene polymorphism affects the onset of diabetic neuropathy in humans. Multiple GLO I gene polymorphisms are known to exist, some of which have decreased enzymatic activity, suggesting that there are individual differences in GLO I activity. A recent report showed a significant correlation between decreased GLO I activity in serum samples and painful diabetic neuropathy (Skapare *et al.,* 2013). In addition, Groener *et al.,* reported that the incidence of diabetic neuropathy was predominantly higher in type 2 diabetic patients with a mutant homozygous for C332C in the GLO I gene. Thus, GLO I activity may be a useful biomarker for diagnosing diabetic neuropathy.

Molecules That Participate in the Progression of Inflammation

Toll-Like Receptor (TLR)

Toll-like receptors (TLRs) are receptors that play an important role in the innate immune response (Miyake, 2007); among these, TLR4 is associated with many diseases of the immune system (Garcia *et al*., 2020). On the other hand, in the peripheral nerves of diabetic humans and animals, infiltration of inflammatory cells, such as macrophages and lymphocytes, is observed, and the production of cytokines, such as tumor necrosis factor (TNF-α) and interleukin (IL), is enhanced (Yamagishi *et al*., 2008). TLR2/4-knockout mice are less likely to develop neuropathy due to the ingestion of a high-fat diet, suggesting a relationship with the pathogenic mechanism of diabetic neuropathy (Elzinga *et al.*, 2019).

Zhu *et al.,* (2015) investigated the expression levels of TLR4 and its downstream genes in human peripheral blood mononuclear cells collected from patients with type 2 diabetes. It was observed that the expression levels of TLR4 were increased in diabetic patients who developed neuropathy compared to those in healthy subjects and diabetic patients who did not develop neuropathy. Furthermore, the levels of TNF-α and IL-6 in serum were also significantly increased in diabetic patients who developed neuropathy. These results suggest that TLR4 may be a useful marker for diabetic neuropathy.

Adiponectin

Adiponectin is an adipocytokine secreted by adipocytes and is a 30 kDa protein. Adiponectin plays various roles in human metabolism, such as lipid regulation, glucose metabolism, and increased insulin sensitivity (Maeda *et al.,* 2020). Several studies have investigated the relationship between serum adiponectin levels and diabetic nerve injury. Although there is an association between them, corroborating results have not always been obtained. For example, a cross-sectional study in India examined serum adiponectin in 487 patients with type 2 diabetes and found that diabetic patients with neuropathy had significantly higher levels of adiponectin than those without it (Rodriguez *et al*.,

2016). Similarly, a study by Pradeepa *et al*., reported that a high level of adiponectin was associated with an increased incidence of neuropathy (Pradeepa *et al.*, 2015). On the other hand, although serum adiponectin levels are associated with diabetic neuropathy, the KORA F4/FF4 study reported that decreased, rather than elevated, serum adiponectin levels were associated with diabetic peripheral neuropathy incidence (Herder *et al.*, 2017). Therefore, these conflicting studies suggest that different genetic backgrounds and target ages due to diversity in the ethnic composition of participants affect adiponectin levels in serum. However, these results also suggest that there is a relationship between serum adiponectin levels and the development of diabetic neuropathy. Therefore, adiponectin remains one of the promising biomarkers for the future, and it is expected that more standardized research will be conducted across different racial groups.

MicroRNAs (miRNAs)

miRNAs are non-coding single-stranded RNA, about 20–22 bases in length, which control gene expression by suppressing degradation or translation by complementarily binding to the 3' untranslated region of the target mRNA (Kato *et al.,* 2013). miRNAs are attracting attention as new biomarkers, as their expression patterns are relevant to pathophysiological processes. miR-146a is one of the miRNAs whose expression levels are reduced in the serum samples of diabetic patients (Baldeón *et al.*, 2014). Wang *et al.,* (2014) reported that hyperglycemia downregulated miR-146a expression and elevated interleukin-1 receptor activated kinase (IRAK1) and tumor necrosis factor receptor-associated factor 6 (TRAF6) levels in dorsal root ganglia (DRG) neurons. Furthermore, miR-146a has been shown to play an important role in mediating DRG neuron apoptosis under hyperglycemic conditions. Other candidate miRNAs that could be useful biomarkers are being explored. Massaro et al. recently performed the miRNA expression profiling of peripheral blood mononuclear cells collected from 63 diabetic patients, classified them according to the type of complication (Massaro *et al*., 2019) and identified the miRNA groups that were specifically upregulated in the diabetic neuropathy group (miR-125a-5p, miR-145-3p, miR-99b-5p, and miR-873-5p). Furthermore, serum miR-518d-3p and miR-618 were upregulated in patients with diabetic peripheral neuropathy compared to individuals without microvascular complications in a cohort study of patients with type 1 diabetes (Santos-Bezerra *et al.,* 2019). These data suggest that circulating miRNAs may serve as potential biomarkers for the diagnosis of diabetic neuropathy in the future.

Neuron-Specific Enolase (NSE)

Nerve-specific enolase (NSE) is a glycolytic enzyme that exists specifically in nerve tissue and shows a high positivity rate, especially in small-cell lung cancer and neuroblastoma. Therefore, NSE is widely used as a tumor marker for detecting these diseases (Kulpav *et al.*, 2002). Li *et al.,* (2013) investigated the relationship between blood NSE levels and diabetic neuropathy because the synthesis of these enzymes may be altered during the process of degeneration and regeneration of peripheral nerves due to the oxidative stress caused by chronic hyperglycemia. The serum NSE levels were slightly higher in the type 1 and type 2 diabetic groups than in the control group. In particular, they increased in the group with neuropathy. This relationship was independent of fasting blood glucose, HbA1c, duration of illness, diabetic type, age, gender, renal function, and serum NSE levels, which were associated with the degree of neuropathy. In addition, it has recently been reported that the value decreased not only with the onset and progression but also with the improvement in neuropathy in response to treatment (Anju *et al.,* 2020). This result suggests that NSE may be a marker for predicting therapeutic effects as well as for early detection of diabetic neuropathy; however, future studies, including large-scale clinical trials, are awaited.

Semaphorins

Semaphorins are a large family of proteins originally identified as axon guidance factors of the developing nervous system. They are multifunctional proteins that play important roles in various biological processes, such as immune responses, organogenesis, and angiogenesis (Nishide and Kumanogoh, 2018). Since these proteins are also involved in axon guidance during the regeneration process after damage to peripheral nerves, they may be ideal candidates as biomarkers for diabetic neuropathy. Several studies reported that these proteins were induced in peripheral nerves distal to a transection or crush injury in a ligation rat model (Ara *et al.,* 2004). In addition, the administration of recombinant Semaphorin 3A (Sema3A) protein attenuated mechanical allodynia and heat hyperalgesia in chronic constriction injury (CCI) rats (Hayashi *et al.,* 2011). In line with these observations, Wu et al. reported that higher Semaphorin 3A expression was accompanied by reduced intraepidermal nerve fiber density in the skin of diabetic patients compared with that in control subjects (Wu *et al.,* 2018).

Heat Shock Protein (HSP27)

HSP27 is a small heat shock protein that plays an important role in cell protection under stress. Increased levels of HSP27 have been observed in DRG cells of the spinal cord in diabetic mice (Kamiya *et al*., 2005). In addition, this protein plays a role in protecting Schwann cells from apoptosis. Although several studies have investigated the relationship between serum HSP27 levels and patients with diabetic neuropathy (Pourhamidi *et al.*, 2014) these results are conflicting. One study reported a correlation between blood HSP27 levels in patients and the occurrence of diabetic polyneuropathy. However, other reports for HSP27 were not in agreement. Further investigation, such as prospective cohort studies, is necessary to clarify this.

2.11.3 Diagnosis of Diabetic Nephropathy

Diabetic kidney disease is one of the main causes of increased morbidity and mortality in patients with diabetes mellitus (DM) (Stanton, 2014). About 20%-40% of patients with DM, both types 1 and 2, will develop diabetic kidney disease. If not treated properly, this will reach an advanced stage, known as end-stage kidney disease (ESRD) (Persson and Rossing, 2018). Currently, the urinary albumin-creatinine ratio (UACR) and estimated glomerular filtration rate (eGFR) are two indicators that are commonly used in the diagnosis of diabetic kidney disease (Colhoun and Marcovecchio, 2018; Ihim *et al*., 2019). Several studies that have been conducted on the UACR value showed that not all diabetic kidney disease patients experience an increased value in the early stages of the disease, which indicates that the UACR value is not sensitive enough as a marker in the early phase of diabetic kidney disease (Said and Nasr, 2016). On the contrary, calculation of the eGFR value using serum creatinine is only accurate when the eGFR value is <60 mL/min/1.73 m2, in which case half of the kidney function may have already been lost (Bjornstad *et al.*, 2015). Therefore, a more sensitive and specific biomarker than the two biomarkers currently used is highly needed, to accurately predict diabetic kidney disease in the early phase.

In the past decade, many new biomarkers associated with diabetic kidney disease have been discovered; these include proteins, metabolite products and genes. Most of the biomarkers found were protein, a macromolecule that functions in various biological processes in the body. Given the important role of protein in the body, a method that can provide information on protein dysregulation would be useful in understanding the pathogenesis of a disease (Pena *et al*., 2016). The proteomic method is currently one of the most promising in discovering new biomarkers (Pena *et al*., 2016). The method comprises a process of analyzing proteomes and proteins, which are expressed in various biological fluids such as urine, plasma, and serum. In recent years, several biomarkers for diabetic kidney disease have been identified. Protein in the urine can reflect damage occurring in the kidneys, such as kidney injury molecule-1 (KIM-1), which plays a role in renal tubular damage (Pena *et al*., 2016). The development of diabetic kidney disease involves various mechanisms. Therefore, a single biomarker is not sufficient to describe the entire process taking place. Instead, a biomarker panel consisting of several proteins and peptides is considered more representative of the various disease development mechanisms and a more accurate biomarker (Pena *et al*., 2016).

Biomarkers Related to Tubular Damage

Vitamin D-Binding Protein (VDBP)

This is a plasma protein that plays a role in various physiological functions of the body, including as a carrier for vitamin D3 metabolites in the blood circulation; the binding and absorption of actin; and inflammation and the immune system (Bouillon, 2011). Tian *et al.,* (2014) revealed that increased excretion of VDBP in urine was associated with tubular dysfunction. Therefore, it is thought that an increase in VDBP excretion can also occur in patients with diabetic kidney disease. In their study, it was shown that the concentration of VDBP in urine significantly increased in type-2 DM patients with various levels of albumin secretion when compared with the healthy control group. These results were similar to those of previous studies. Apart from an increase in urine, VDBP concentrations were also significantly increased in the microalbuminuria group. VDBP in urine and serum shows a relationship with the UACR (Fawzy and Abu, 2018).

Kidney Injury Molecule- 1 (KIM-1)

KIM-1 is a 38.7-kDa type I transmembrane glycoprotein with an extracellular immunoglobulin-like domain topping a long mucin-like domain. As usual, it is expressed at low levels in the kidney and other organs, but it is significantly upregulated when the kidney undergoes injury, especially after ischemia reperfusion injury. In humans, proximal tubule cells are the main locations where KIM-1 expression is up regulated. KIM-1 plays an important role in both kidney injury and the associated recovery processes. Hence, some studies have proposed urinary kidney injury molecule- 1 (uKIM-1) as a sensitive and specific marker of AKI as well as a predictor of outcome (Bonventre, 2008). Although an increasing number of related studies have been conducted in recent years, additional clinical research and trials are required to support the clinical application of KIM-1 in the early diagnosis of AKI. It is thought to have the potential to be used as a marker to determine renal tubular damage in diabetic kidney patients (Anadón *et al.,* 2014). Gohda *et al*., (2019) found that the KIM-1 concentration in serum was significant in patients with renal insufficiency, showing an association with better eGFR value than KIM-1 in urine. In addition, KIM-1 in serum also has a relationship with the duration of suffering from diabetes; it was found to be elevated in patients with diabetes duration of <5 years. The results indicate that KIM-1 has the potential to be used as a biomarker in the early phase of diabetic kidney disease (Khan *et al.*, 2019).

Neutrophil Gelatinase Associated Lipocalin (NGAL)

Neutrophil gelatinase associated lipocalin (NGAL), also known as lipocalin-2, is a recently identified adipokine that belongs to the superfamily of lipocalins. It is a glycoprotein involved in transmembrane transportation of lipophilic substances (Kalousek *et al.*, 2006). It is found in activated neutrophils and several other tissues including the liver, kidney, adipocytes, and macrophages. Kidney tubular cells may produce NGAL in response to various injuries. It is a newly recognized marker of nephropathy. NGAL was suggested to be a biomarker of acute kidney injury (AKI) even in the setting of chronic kidney disease. It

has a strong association with albuminuria (Sise *et al.,* 2009). Although NGAL is normally present in the circulation, only a very small amount is expressed in the kidneys and excreted in the urine. Systemic NGAL is freely filtered through the glomerulus, but it is totally reabsorbed by the renal proximal tubules. Following ischemia and AKI, NGAL is one of the earliest substances that are released into the urine. Due to increased GFR in SCD, it is unclear whether the levels of this biomarker would be elevated or subnormal. Devarajan and coworkers have identified NGAL as a novel sensitive marker of renal tubular damage in acute and chronic nephropathy (Devarajan, 2010).

Megalin

Megalin is a 600-kDa single transmembrane receptor protein. It belongs to the low-density lipoprotein receptor family. Megalin is responsible for the normal tubular reabsorption of virtually all filtered proteins, mediating the recovery of essential substances that otherwise would be lost in the urine (Christensen *et al.,* 2012). Megalin binds a very wide range of ligands, including carrier proteins, peptides, hormones, signaling molecules, enzymes, immune-related proteins, etc. The known ligands of megalin normally filtered in the glomeruli include retinol-binding protein, transcobalamin-B12, insulin, α1- and β2-microglobulin, EGF, albumin, lysozyme, cytochrome c, cystatin C, liver-type fatty acid-binding protein (L-FABP), α-amylase, and prolactin. Other ligands, which are normally only filtered in very limited amounts, are myoglobin, hemoglobin, and immunoglobulin light chains (Christensen *et al.,* 2012). Additionally, nonphysiological ligands are also filtered, including drugs and toxins such as gentamicin, polymyxin B, and aprotinin (Christensen *et al.,* 2012). Mutations in aprotinin decrease its affinity toward megalin, indicating that binding is charge dependent and favored by cationic sites on the ligands. However, many ligands of megalin are anionic proteins, suggesting that binding depends on the distribution of charge rather than the overall isoelectric point. Megalin is a multiligand, endocytic receptor expressed in kidney proximal tubule luminal membranes and apical endocytic compartments. Absence of megalin leads to proximal tubule dysfunction with tubular proteinuria and a significant reduction in the apical, endocytic apparatus of PTECs.

Inflammation-Related Biomarkers

Biomarkers of the inflammatory process also show promising results in predicting the development of diabetic kidney disease (Xiang *et al.,* 2019).

MCP-1 (Monocyte Chemoattractant Protein-1)

MCP-1 is a secreted protein which specifically attracts blood monocytes and tissue macrophages to its source, via interaction with CCR2, its cell surface receptor. Kidney cells produce MCP-1 in response to a variety of proinflammatory stimuli and predictably, its expression has been identified in kidney diseases which involve significant inflammation, which include diabetic nephropathy (Amann *et al.,* 2003). Elements of the diabetic milieu are known to induce MCP-1 mRNA synthesis and protein secretion by cultured renal parenchymal cells, suggesting that the onset of diabetes can provoke renal macrophage recruitment. This plays a role in the recruitment of macrophages and monocytes, was found to be increased in people with DM without albuminuria. A significant increase occurred in the levels of MCP-1 in the urine of type-2 DM patients with macroalbuminuria compared with other groups of type-2 DM patients and healthy controls (Kim and Tam, 2011).

High levels of glucose have been shown to stimulate MCP-1 production by human and mouse mesangial cells through a pathway which involves activation of PKC, increased levels of oxidative stress, and the activation/nuclear translocation of the transcription factor nuclear factor-κB (NF-κB) (Kanamori *et al*., 2007). This stimulatory effect of high glucose in mesangial cells is further enhanced by the presence of advanced glycation end products (AGEs) or mechanical stretch. A variety of AGEs are also capable of stimulating MCP-1 production by mesangial cells, which involves interaction with the receptor for AGEs (RAGE) with subsequent generation of oxidative stress via activation of peroxisome Kidney epithelial cells, including glomerular podocytes and tubular cells, also make MCP-1 in response to high glucose and AGEs. Exposure to high glucose rapidly induces MCP-1 mRNA and protein release by cultured mouse podocytes, which is inhibited by treatment with all-trans retinoic acid (Gruden *et al*., 2005).

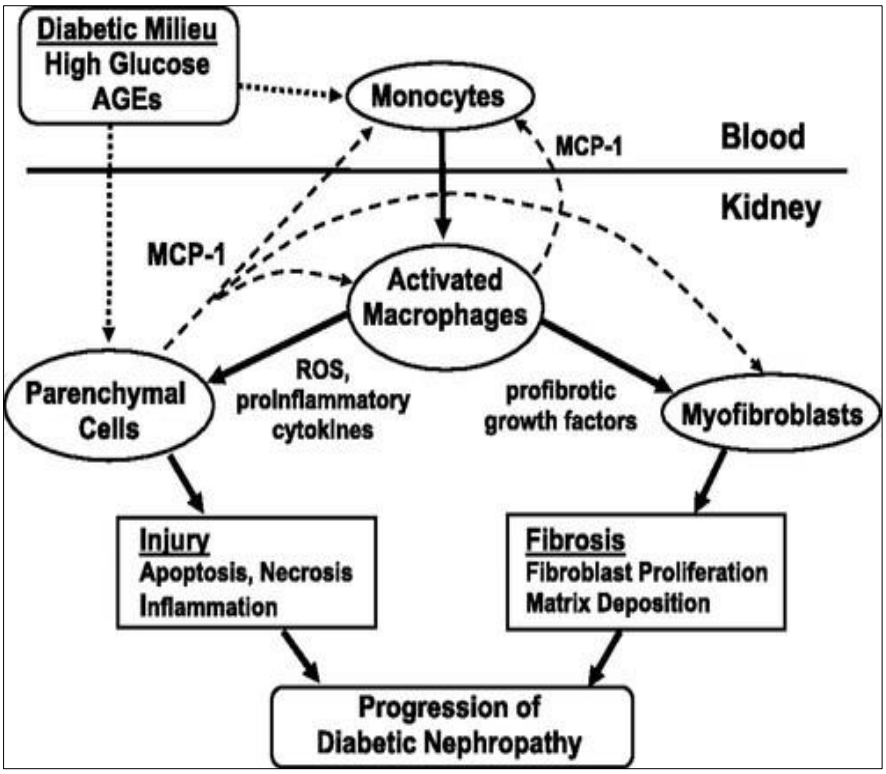

Fig. 9: Involvement of MCP-1 in Diabetic nephropathy

Adiponectin

This functions as an anti-inflammatory agent, decreases in concentration as diabetic kidney disease develops. Adults with type-1 DM experienced a significant increase in adiponectin than healthy adults. The difference in concentration between the two groups also remained significant during the follow-up period of 6 years after adjustments for eGFR and albumin excretion ratio. In addition, diabetic kidney disease patients with a rapid decrease in eGFR values also had higher adiponectin concentrations than type-1 DM patients without diabetic kidney disease (Bjornstad *et al*., 2017).

Biomarkers Related to Glomerular Damage

Beta-2 Microglobulin (B2M)

This has shown a promising ability to detect glomerular damage in diabetic kidney disease. B2M concentrations increased in diabetic patients with normal kidney function (eGFR ⩾ 90 mL/min/1.73 m2) (Jiang *et al.*, 2017).

Glypican-5 and Smad1

These show involvements in the occurrence of glomerular morphological changes, especially in mesangial cell dysfunction (Okamoto *et al*., 2015). An in vivo study found that GPC5 levels were significantly elevated in mice with induced diabetes, especially in the mesangial cells and kidney podocytes (Okamoto *et al*., 2015). Diabetic patients experienced a significant increase in GCP5 concentrations compared to the healthy control group. After a 52-week follow-up period, in the diabetic kidney disease patients, GCP5 was estimated to have a strong correlation with decreased eGFR values ($r = -0.786$) and albumin secretion ($r = 0.346$). Therefore, GCP5 has the potential to be used as a biomarker for diabetic kidney disease. However, further studies are needed regarding the mechanism of the association of GCP5 with other clinical parameters (Li *et al.,* 2019).

In the development of diabetic kidney disease, Smad1 plays a role in the overproduction of type-IV collagen in mesangial cells in animals, which is induced by diabetes acting on the TGF-β receptor. Type-IV collagen is a component that plays a major role in the expansion of the mesangial matrix in diabetic kidney disease. A study showed that high Smad1 concentrations correlated with the rate of mesangial cell expansion in diabetic kidney disease (Doi *et al*., 2018).

Angiopoietin-Like 4 (ANGPTL4)

This also thought to play a role in the breakdown of glomerular podocytes. Physiologically, it plays a role as a regulator in lipid metabolism by inhibiting lipoprotein lipase (LPL) activity and also plays a role in the pathophysiological mechanisms of cardiovascular disease and metabolic syndrome. Clement *et al*., (2010) explained that ANGPTL4 plays a part in the proteinuria process in nephropathic syndrome, in which the high concentration of ANGPTL4 produced by podocytes can cause changes in the glomerular basement membrane and reduce the ability of the podocyte diaphragm slit in experimental animals.

Increased secretion of ANGPTL4 in podocytes causes a decrease in the function of the podocyte diaphragm slit. In a study of type-2 DM patients by Al Shawaf *et al*., (2019) the plasma ANGPTL4 concentration was significantly higher in diabetic kidney disease patients compared to type-2 DM patients and the control group. In addition, ANGPTL4 was found to have a correlation with the eGFR value and albumin–creatinine ratio.

2.11.4. Diagnosis of Diabetic Foot Ulcer (DFU)

Procalcitonin

Procalcitonin (PCT), a polypeptide released by thyroid C cells, liver, lung, and kidney parenchymal cells, is composed of 116 amino acids as a precursor of calcitonin, which plays an important role in the diagnosis of bacterial infection as a biomarker (Velissaris *et al.*, 2018). Umapathy *et al*. (2018) carried out a clinic study with 185 T2DM patients, and divided their into three groups, which were T2DM patients without DFU (WDFU), T2DM patients with infectious DFU (IDFU), and T2DM patients with noninfected DFU (NIDFU). The blood analysis was carried out subsequently and it was reported that PCT might be a key indicator for the diagnosis of IDFU patients. It showed that in IDFU patients, PCT (0.99) had the largest value of the area under the receiver operating characteristic curve (AUCROC), followed by C-reactive protein levels (CRP, 0.78), white blood cell count (WBC, 0.76), and erythrocyte sedimentation rate (ESR, 0.74). When the critical value was 0.5 ng/mL, the sensitivity of PCT was 54 %, and its specificity was 100 %, as well as for the diagnosis of IDFU, the positive predictive value was 100 %, and the negative predictive value of was 12 %. Besides, PCT levels in the peripheral circulation were positively correlated with T-helper-1- cell cytokines (e.g., interferon-γ and interleukin-28A) and subtype cytokines 17 (e.g., interferon-γ1 and interleukin-29). Moreover, comparing IDFU and NIDFU, the PCT levels difference between them was up to 7 times, better than the traditional indicators, i.e., CRP, WBC, and ESR, etc., and had higher sensitivity and specificity. Therefore, PCT can be used as an important biomarker for IDFU diagnosis.

Pentraxin-3

Pentraxin-3 (PTX-3) is a soluble pattern recognition receptor, which is synthesized by mononuclear phagocytes, fibroblasts, myeloid dendritic cells, granulosa cells, mesangial cells, endothelial cells, smooth muscle cells and adipocytes locally at the inflammatory site. Therefore, its level may more directly reflect vascular inflammation. In the process of inflammatory, a plenty of PTX-3 is produced in the vascular wall, which act as an endothelial regulator in thrombosis and ischemic vascular disease, and binds to angiogenic fibroblast growth factor-2, thereby inhibiting angiogenesis and restenosis (Abu *et al.*, 2013). Ozer *et al*. (2019) concluded that PTX-3 is a valid marker for diagnosis of IDFU.

C-reactive protein (CRP)

C-reactive protein (CRP), a hepatic-originated plasma protein, is a key element of any inflammatory reaction and a member of the pentraxin superfamily. As a result of tissue damage or infection, the plasma levels of CRP may rapidly increase to more than 1000-folds above normal values, therefore it is widely used a monitor marker in the acute phase, responding to tissue damage, infection and inflammation in routine clinic. Recently, it is a typical disease marker of cardiovascular diseases for its remarkable significance in clinic and pathology. The role of CRP, as a research and therapeutic reagent, has been fully clarified by the current booming of researches in various diseases and related conditions. Studies have shown that elevated CRP levels are associated with diabetes (McFadyen *et al*., 2018).

Interleukin

Interleukins (ILs), produced by blood monocytes and tissue macrophages, are a group of cytokines that are critical important for the function of the immune system -- both innate and adaptive. When the body is infected, ILs are secreted onto target cells and bind to the signals on the surface that activate the target cells, altering cell behavior. ILs levels would be elevated in patients with DFU along with the development of insulin resistance, abnormal healing and decreased with the healing of ulcers (Zubair and Ahmad, 2019). Sabuncu *et al*. (2014) selected 20 patients with acute DFU, 21 DM patients without DFU, and 21 healthy volunteers. Blood sample analysis showed that IL-18 in DFU patients and DM patients without DFU was significantly elevated compared to that in healthy subjects ($P < 0.001$ and $P = 0.020$).

Tumor Necrosis Factor-α

Tumor necrosis factor alpha (TNF-α) is one of the major inflammation regulator and a cell signaling protein identified as a key role player in the cytokines network. TNF-α, as a versatile mediator and an important member of the TNF family that is mainly generated by monocytes, macrophages and T-cells, could affect many biological pathways including the cellular/molecular process of adhesion, migration, angiogenesis and apoptosis. The main function of TNF-α is regulating the immune system via the activation of T cells, B cells and macrophages, thereby inducing the expression of other cytokines and cell adhesion molecules. In addition, the role of TNF-α in wound healing is implied by its significant expression in vascular endothelial cells. TNF-α has been reported to have an indirect angiogenic effect, depending on the synthesis of secondary mediators, e.g., vascular endothelial growth factor (VEGF). However, it is difficult to understand the dual angiogenesis (pre/anti) role of TNF-α under different conditions. Overall, in addition to several malignant tumors, TNF-α dysregulation has also connected with a variety of human inflammatory diseases (Salajegheh, 2016). It also induced insulin resistance by attenuating insulin signaling by promoting serine phosphorylation of insulin

receptor substrate 1. B-cell activating factor (BAFF), also included in the TNF-α family (Salajegheh, 2016) indicates the presence of dysfunction in B cells.

2.11.5. Diagnostic Biomarkers for Stroke

S100B

S100B, a glial protein, highly specific to nervous tissue, was one of the first molecules suggested as a candidate to aid IS diagnosis. Serum S100B concentration measured 24 h after symptom onset is significantly higher in stroke patients (posterior circulation IS or infratentorial ICH, no distinction was made in the analysis) than in controls or in patients with vertigo from non-vascular causes (Purrucker *et al*., 2014). However, in addition to prolonged and delayed release into the blood after stroke, S100B levels are also increased in other neurological pathologies such as traumatic brain injuries and extracranial malignancies.

GFAP

GFAP (glial fibrillary acidic protein), another glial protein specific to astrocytes (Eng *et al.*, 2000), is the best candidate to date for differentiating hemorrhage and ischemic stroke. Based on detection of delayed GFAP release in patients with ischemic stroke (maximum concentration reached 2–4 days after ischemic stroke onset), Foerch and his team studied this molecule in different clinical settings and showed promising results (Foerch *et al.*, 2006). In a multicenter clinical study of 205 patients (163 with IS, 39 with ICH and three stroke mimics) diagnostic accuracy was high for differentiating intracerebral hemorrhage from ischemic stroke by GFAP immunoassay on a single blood sample obtained within 4.5 h of symptom onset.

Neuron-Specific Enolase (NSE)

Serum concentrations of NSE (neuron-specific enolase) have been reported to be as significantly raised in stroke patients compared to controls and to correlate with infarct size and stroke symptom severity (Wunderlich *et al.,* 2004). Overall, NSE has a similar discriminatory profile to S100B (high specificity and low sensitivity) (Gonzalez-Garcia *et al.,* 2012). This may in part be due to variable kinetics of release, sometimes peaking 24 h after stroke.

N-methyl-D aspartate receptors (NMDA-R)

Autoantibodies to the glutamate NMDA-R (N-methyl-D aspartate receptors; NR2A/NR2B subunits) associated with neurotoxicity are elevated after stroke and distinguish IS patients (n = 31) from controls 3 h after symptoms onset with 97% sensitivity and 98% specificity (Dambinova *et al.*, 2003). . In a different cohort, plasma levels of NMDA-R NR2A were also shown to be elevated in ischemic strokes when there was no difference observed in patients with cerebral hemorrhage in comparison to controls (Dambinova *et al.*, 2002).

Apo-Lipoproteins

Some members of the apo-lipoprotein family have also been tested as potential biomarkers for IS diagnosis. Apo C-I and Apo C-III concentrations were found to be increased in IS compared to ICH within 6 h of symptom onset and both were reported to have the potential to discriminate IS from ICH. For Apo C-III this was achieved with 94 and 87% sensitivity and specificity, respectively (Allard *et al*., 2004). A panel of nine apo-lipoproteins was tested as a tool to distinguish IS and ICH patients within the first week after symptom onset using a mass spectrometry assay. Apo C-I and Apo C-III reported to provide the best classification power as individual markers but combining Apo C-III and Apo A-I provided the best discrimination overall (AUC = 0.92) (Lopez *et al*., 2012).

Other common biomarkers are: cardiac troponin, creatine kinase, or D-dimer etc.

2.12 Current Advances in the Management of Complications Associated with type 2 DM

Lifestyle management along with pharmacological approaches is crucial to achieve a successful management of diabetes. The pharmacological approach to treat T2DM can be only partly effective in the long-term management of diabetes. Major modifications in the lifestyle of patients along with the interventions through pharmacological approaches are crucial to ensure an effective management of the disease. These include changes in physical activity, dietary modifications, management of stress or associated factors, and improved sleeping patterns. The next few sections of this review will discuss and explore the potential of these factors in the management of diabetes when followed in parallel with the pharmacological management of the disease.

The guidelines for the pharmacological management of diabetes provided by American Diabetes Association suggest that metformin be prescribed as the initial intervention to T2DM patients. However, the same guideline also indicates that vitamin B12 deficiency is a prominent side effect observed in metformin consumers and a periodic vitamin B12 measurement is required in such patients (American Diabetes Association, 2019). Furthermore, metformin is also notorious for causing lactic acidosis, especially in patients with kidney disease, liver injury, or other CVS complications that create a low level of oxygen in circulation. For T2DM patients with cardiovascular or CKDs, the guidelines recommend adding sodium-glucose cotransporter 2 (SGTL2) inhibitors and/or glucagon-like peptide 1 receptor agonists along with hypoglycemic agents (American Diabetes Association, 2019).

The employability of SGTL2 inhibitors with almost all classes of hypoglycemic agents makes them ideal candidates to be combined when dual and triple combination therapies are warranted (Kalra *et al.*, 2018).

In an ideal scenario, a drug used in combination should be able to reverse the pathology with an improved overall health status of the patient and ensure that no new complications arise due to the existing management strategies. In case of T2DM, drug combination should not only be able to just merely reduce the glycosylated hemoglobin levels (HbA1C) but also an improved overall metabolic condition of the patient is expected through such interventions. The combination of SGTL2 inhibitors with metformin may have proved beneficial in curbing hyperglycemia that cannot be controlled by metformin alone (Kalra *et al.*, 2018) but the adverse effects associated with the SGTL2 inhibitors still remain unresolved.

Genital infections caused by SGTL2 inhibitors due to high glycosuria still remain an unfocussed aspect while prescribing such combinations. In addition, during the event of excessive osmotic diuresis caused by SGTL2 inhibitors, a low extracellular fluid volume and subsequent hypotension is another complication that may arise (Hsia *et al.*, 2017). Multiple reports have also raised concerns regarding the use of SGTL2 inhibitors in diabetes due to their substantial involvement in causing diabetic ketoacidosis (Peters *et al.,* 2015). Two separate reports published in 2015 claimed that canagliflozin, an SGTL2 inhibitor is implicated in pancreatitis in T2DM patients. GLP-1 agonists are also a preferred class of adjuvant hypoglycemic agents that are combined with first-line hypoglycemics (Filippatos *et al*., 2015). Apart from gastrointestinal disorders (nausea, vomiting, and constipation), infections and acute renal injury, a major raising concern regarding the use of GLP-1 agonists is their association with pancreatitis (Filippatos *et al*., 2015).

Cases of acute pancreatitis are reported with the use of liraglutide and exenatide (Lee *et al*., 2011). More importantly, recent reports also raise concerns regarding the long-term reliance on incretin-based therapies due to frequently reported cases of their association with pancreatitis and pancreatic cancer. Studies based on FDA Adverse Events Reporting System demonstrated that incretin-based therapies are associated with the increased incidences of pancreatic and thyroid cancer. Exenatide use is also positively associated with the incidences of bone fractures (Su *et al*., 2015).

2.12.1 Physical Activity

Physical activity is positively associated with controlled glycemic levels among T2DM patients. Moderate but daily physical activity has been found to be an effective way to control the long-term manifestations of diabetes. These include walking, gardening, and performing common household chores. Walking is the most effective physical activity in T2DM, as it allows significant glycemic control with limited physical burden in patients who are already physically weak (Hamasaki, 2016). Moreover, a much warranted lifestyle alteration in T2DM patients are changes in sedentary patterns. Sedentary behavior leads to considerably low expenditure of energy. An extended sedentary period in T2DM patients is also associated with uncontrolled glycemic levels. A reduced sedentary time, therefore, is crucial in diabetes patients, which can be achieved by increasing the physical work (Colberg *et al.,* 2016). In addition, regular aerobic exercise is acknowledged to improve HbA1c levels in patients with diabetes. Aerobic exercise tends to improve health outcomes in patients through multiple mechanisms that include the manifold increase in mitochondrial densities, improved sensitivity to insulin, improved compliance of blood vessels, and lung functions with enhanced cardiac output (Garber *et al*., 2011).

2.12.2 Dietary Changes and Medical Nutrition Therapy

Insulin resistance and subsequent appearance of T2DM are closely linked with high intake of sugars, fried food, and red meat. On the contrary, reduced risk of T2DM development is observed in case of intake of vegetables having high content of antioxidants, fiber, and other nutrients (Villegas *et al*., 2008). The average energy intake of diabetes patients differs with their obesity status. Usually, for a nonobese diabetic patient, an average energy intake of 1,500–2,500 calories per day is recommended, while for obese patients, the average calorie intake is reduced to 800–1,500 calories per day. Limited intake of refined sugars is highly recommended in T2DM patients. Non-nutritive sweeteners (aspartame, saccharine, etc.) can be the good substitutes for sugar in such patients. Moreover, the restricted intake of food rich in saturated fats and cholesterol and its replacement with food rich in polysaturated fats is also recommended. In addition, changes in eating patterns, such as dividing meals into small fractions over the day rather than taking 1 or 2 large meals can prevent vigorous postprandial peaks in blood glucose levels (Asif, 2014). Strict adherence to controlled diet with sufficient physical activity is largely associated with lower incidence of diabetes. Incorporation of Paleolithic diet (a diet rich in lean meat, fish, fruits, and vegetables) in the daily routine of diabetic patients results in marked improvement in glucose handling. The employment of nutritional therapy in the management of diabetes is also widely suggested. Nutritional therapy is an approach to treat a disease through the modifications in food and nutrition intake.

The application of evidence-based nutrition care therapy in diseased patients by a qualified and registered dietician is termed as medical nutrition therapy. Reduced reliance on oral hypoglycemic therapy is evident in diabetes patients receiving nutritional therapy (Franz and MacLeod, 2018). Also, considerable improvements in clinical outcomes are observed in diabetes patients receiving intensive nutritional education by registered dietician in comparison to patients receiving basic nutrition information (BE). Taken together, simple but profound changes in dietary pattern in diabetic patients is a potential approach to curb

the long-term implications of diabetes. Moreover, successful application of nutritional therapy in individuals with diabetic conditions can be a lucrative approach to achieve a better management of diabetes with improved health outcomes.

2.12.3 Chronopharmacology

Pharmacokinetics and pharmacodynamics (PK-PD) are markedly influenced by daily rhythms in physiology. This phenomenon is termed chronopharmacology (Dallmann *et al*., 2016). Indeed, the pathogenesis of diabetes largely depends on hormonal and body homeostasis. Chronopharmacology should be considered as part of treatment strategies for diabetes. The failing β-cells in T2DM do not lose all their capability to respond to glucose. Insulin secretion in response to stimulation through amino acids or other hormones such as glucagon-like peptide 1 (GLP-1), remains preserved. The levels of leptin (satiety hormone) in blood generally remain higher between midnight and early morning, conceivably to suppress appetite during the night. Moreover, the levels of ghrelin increase with increase in the duration of sleep. In addition, the time dependency in GLUT4-mediated glucose uptake is also a function of circadian variation (Miyazaki *et al*., 2011). Furthermore, meal timings can modify the diurnal rhythm of blood leptin levels. Both ghrelin and leptin work with other hormones and HPA axis through feedback loops to indirectly affect the psychophysiological satisfaction in diabetic patients (Klok *et al.*, 2007). Chronopharmacology, therefore, may considerably affect diabetic pathophysiology and PK-PD of administered drugs.

2.12.4 Management of Diabetic Retinopathy

Pharmacologic therapy is usually used in the management of diabetic retinopathy. They include;

Triamcinolone: Administered intravitreally; corticosteroid used in the treatment of diabetic macular edema

Bevacizumab: Administered intravitreally; monoclonal antibody that can help to reduce diabetic macular edema and neovascularization of the disc or retina

Ranibizumab: Administered intravitreally; monoclonal antibody that can help to reduce diabetic macular edema and neovascularization of the disc or retina (Bhavsar, 2021).

2.12.5 Management of Diabetic Neuropathy

Key components of the management of diabetic neuropathy include the following:

- Foot care, including regular follow-up, patient education, and referral as appropriate.
- Tight, stable glycemic control (most important for slowing progression of neuropathy).
- Pain management (eg, with pregabalin, gabapentin, sodium valproate, dextromethorphan, morphine sulfate, tramadol, oxycodone, duloxetine, topical capsaicin, transdermal lidocaine)
- Treatment of diabetic gastroparesis (eg, with erythromycin, cisapride, metoclopramide, polyethylene glycol 3350, tegaserod

Surgical Treatment May Be Considered as follows:

- Aggressive debridement or amputation for recalcitrant foot necrosis or infection
- Jejunostomy for intractable gastroparesis
- Implantation of a penile prosthesis for ongoing impotence
- Bracing, special boots, or, in some cases, surgery for Charcot foot
- Pancreatic transplantation for diabetes with end-stage renal disease

Treatment for Cataracts

Surgery is the only treatment for cataracts. However, for less severe cataracts, it might help a person to:

- get an altered eyeglass prescription
- use a brighter light for tasks such as reading
- Add anti-glare coatings to eyeglass lenses (Eagle, 2021).

2.13 Role of Supplements in the Management of Complications Associated with Type 2 Diabetes Mellitus

A healthy diet, physical activity, and maintaining a healthy weight are the first, and sometimes, most important part of diabetes treatment. However, when those are not enough to maintain blood sugar levels, alternative treatment would be tried out. People with diabetes have tried numerous herbs and supplements to improve their diabetes. These alternative treatments are supposed to help control blood sugar levels, reduce resistance to insulin, and prevent diabetes-related complications.

Some supplements have shown promise in the management of diabetes and development of complications associated with it. However, supplements are not in themselves drugs and therefore cannot replace standard diabetes treatment. Serious adverse effects could result from abusing supplements (The Healthline Editorial Team, 2020).

These supplements include:

Cinnamon

Chinese medicine has been using cinnamon for medicinal purposes for hundreds of years. It has been the subject of numerous studies to determine its effect on blood glucose levels. A 2011 study has shown that cinnamon, in whole form or extract, helps lower fasting blood glucose levels. More studies are being done, but cinnamon is showing promise for helping to treat diabetes (The Healthline Editorial Team, 2020).

Chromium

Chromium is an essential trace element. It is used in the metabolism of carbohydrates. However, research on the use of chromium for diabetes treatment is mixed. Low doses are safe for most people, but there is a risk that chromium could make blood sugar go too low. High doses also have the potential to cause kidney damage.

Vitamin B-1

Vitamin B-1 is also known as thiamine. Many people with diabetes are thiamine deficient. This may contribute to some diabetes complications. Low thiamine has been linked to heart disease and blood vessel damage. Thiamine is water-soluble. It has difficulty getting into the cells where it's needed. However, benfotiamine, a supplemental form of thiamine, is lipid-soluble. It more easily penetrates cell membranes. Some research suggests that benfotiamine can prevent diabetic complications. However, other studies have not shown any positive effects (The Healthline Editorial Team, 2020).

Alpha-Lipoic Acid

Alpha-lipoic acid (ALA) is a potent antioxidant. Some studies suggest it may:

- reduce oxidative stress
- lower fasting blood sugar levels
- decrease insulin resistance

However, more research is needed. Furthermore, ALA needs to be taken with caution, as it has the potential to lower blood sugar levels to dangerous levels.

Bitter Melon

Bitter melon is used to treat diabetes-related conditions in countries like Asia, South America, and others. There is a lot of data on its effectiveness as a treatment for diabetes in animal and lab studies. However, there is limited human data on bitter melon. There are not enough clinical studies on human. The human studies currently available are not of high quality.

Green Tea

Green tea contains polyphenols, which are antioxidants.

The main antioxidant in green tea is known as epigallocatechin gallate (EGCG). Laboratory studies have suggested that EGCG may have numerous health benefits including:

- lowering cardiovascular disease risk
- prevention of type 2 diabetes
- improving glucose control
- enhancing insulin activity

Studies on diabetic patients have not shown health benefits. However, green tea is generally considered safe.

Resveratrol

Resveratrol is a chemical found in wine and grapes. In animal models, it helps prevent high blood sugar. Animal studies have also shown that it can reduce oxidative stress. However, human data is limited. It is too soon to know if supplementation with resveratrol helps with diabetes (The Healthline Editorial Team, 2020).

Magnesium

Magnesium is an essential nutrient. It helps regulate blood pressure. It also regulates insulin sensitivity. Supplemental magnesium may improve insulin sensitivity in diabetics. A high magnesium diet may also reduce the risk of diabetes. Researchers have found a link between higher magnesium intake, lower rates of insulin resistance, and diabetes.

Chromium

Chromium is metal and an essential trace mineral. It is thought to help reduce blood sugar levels. It is naturally occurring in meat, fish, fruits, vegetables, spices, and whole-wheat and rye breads. As a supplement, it is sold as chromium picolinate, chromium chloride, and chromium nicotinate.

Omega-3 Fatty Acids

These come from foods such as fish, some vegetable oils (canola and soybean), walnuts, and wheat germ. Omega-3 supplements are available as capsules or oils. However, a review published in October 2015 in the journal PloS One showed that omega-3 fatty acids lower triglycerides but do not affect blood glucose control or total cholesterol. In addition, the University of Maryland Medical Center in Baltimore notes that omega-3 fatty acids from fish act to raise HDL ("good") cholesterol in people with diabetes, while omega-3s from flaxseed oil may yield the same benefit (Oreinstein, 2017).

Others Dietary Sources:

Previous studies show that dietary sources including Cucumis sativus (cucumber), *Glycine max* (Soya bean), *Tetracarpidium conophorum* nuts (Nigerian walnuts), *Gongronema latifolium* leaves (Utazi), Moringa oleifera (Analike *et al*., 2017; Ezeodili *et al*., 2017; Ogbodo *et al*., 2017; Nwogor *et al*., 2017; Ogbodo *et al*., 2024a; Maduka *et al*., 2021; Analike *et al*., 2022), have potential antidiabetic effects and may play roles in mitigation of diabetes and its associated complications. These dietary supplements are believed to play roles in the mitigation of diabetes through various mechanisms including improving antioxidant and anti-inflammatory capacity, reversal of dyslipidemia via improved HDL cholesterol and by improving the blood glycosylation among others.

CONCLUSION

The term diabetes mellitus describes diseases of abnormal carbohydrate metabolism that are characterized by hyperglycemia. It is associated with a relative or absolute impairment in insulin secretion,

along with varying degrees of peripheral resistance to the action of insulin. DM has several categories, including type 1, type 2, maturity-onset diabetes of the young (MODY), gestational diabetes, neonatal diabetes, and secondary causes due to endocrinopathies, steroid use, etc. The main subtypes of DM are Type 1 diabetes mellitus (T1DM) and Type 2 diabetes mellitus (T2DM), which classically result from defective insulin secretion (T1DM) and/or action (T2DM). T1DM presents in children or adolescents, while T2DM is thought to affect middle-aged and older adults who have prolonged hyperglycemia due to poor lifestyle and dietary choices. The pathogenesis for T1DM and T2DM is drastically different, and therefore each type has various etiologies, presentations, and treatments. Some of the complications associated with type 2 diabetes mellitus include: neuropathy, nephropathy, retinopathy, ischemic heart disease, stroke, diabetic foot ulcer etc. Several new methods have been introduced for the diagnosis and treatment of complications associated with type 2 diabetes mellitus.

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