Type 2 diabetes mellitus (T2DM), also known as Non-Insulin Dependent Diabetes Mellitus (NIDDM), is one of the common metabolic disorders in the world. T2DM accounts for around 90% of all cases of diabetes mellitus, afflicting millions worldwide. It is a significant global health burden with a steadily increasing prevalence. In T2DM, the response to insulin is diminished, and this is defined as insulin resistance. Risk factors for T2DM are diverse. Some are modifiable, and others are not. Modifiable risk factors include overweight/obesity, lack of exercise or physical inactivity, poor nutrition, etc. Non-modifiable risk factors include age, ethnicity/race, family history, history of gestational diabetes mellitus, etc. The starting points and mainstays of treatment for T2DM are diet and lifestyle modifications such as increased physical activity and stoppage of smoking. In addition to the diet and lifestyle modifications, drugs are also used in the management of T2DM. This study aimed to profile the clinical dynamics of type 2 diabetes mellitus in patients. Current literatures from different databases including MEDLINE, PubMed, EMBASE, CINAHL, Google Scholar, etc. on the topic were searched online and reviewed.

**Keywords:** Clinical dynamics, Type 2 diabetes mellitus, Perspective review, Glycated hemoglobin, Fasting plasma glucose, Impaired fasting glycaemia, Oral glucose tolerance test, Impaired glucose tolerance.

**Introduction**

Diabetes mellitus is a condition defined as a constellation of diseases of metabolic origin. Diabetes mellitus (DM) is a chronic metabolic disorder characterized by persistent hyperglycemia. Several distinct types of DM are caused by a complex interaction of genetics and environmental factors [32]. It is characterized by hyperglycemia which results from defects in the secretion of insulin, the effect of insulin on glucose in the bloodstream or both of them [1]. Depending on the etiology of DM, factors contributing to hyperglycemia include impaired insulin secretion, decreased glucose utilization, and increased glucose production [20]. On the long run, the effects of hyperglycemia on different organs of the body as a result of uncontrolled diabetes mellitus are associated with prolonged damage, malfunction, and collapse of function of different organ systems in the body which mostly include the visual, urinary, nervous, cardiovascular and hematological systems [1]. This perspective review aimed to summarize the current understanding of the clinical dynamics of T2DM with respect to epidemiology, risk factors, etiology, pathogenesis, clinical features, diagnosis, treatment, complications (both acute and chronic) and prognosis.

**Method**

Current literatures from different databases including MEDLINE, PubMed, EMBASE, CINAHL, Google Scholar, etc. on the topic were searched online and reviewed.

**Discussion**

The International Diabetes Federation (IDF) Diabetes Atlas (2021) reported that 10.5% of the adult population of the world (20-79 years) has diabetes mellitus, with almost half unaware that they are living with the condition. By 2045, IDF projections show that 1 in 8 adults, approximately 783 million, will be living with diabetes mellitus, an astonishing increase of 46%. Approximately 537 million adults (20-79 years) are living with diabetes mellitus. 3 in 4 adults with diabetes mellitus live in low- and middle-income countries [42]. In 2021, the International Diabetes Federation (IDF) estimated that sub-Saharan Africa had almost 24 million adults aged 20-79 years who were living with diabetes mellitus with a regional prevalence of 4.5%. However, 54.0% of the people living with diabetes mellitus in the region are undiagnosed. The burden of DM is huge in developing countries as a result of inequitable distribution of medical facilities for early diagnosis and reasonable blood glucose level determination [61].
According to WHO Global Report on Diabetes Mellitus, the global prevalence of diabetes mellitus (aged-standardized) has nearly doubled since 1980, rising from 4.7% to 8.5% in the adult population [79]. This reflects the increasing prevalence of type 2 diabetes mellitus risk factors, particularly obesity. In people with T2DM, 90% are overweight or obese. DM prevalence has risen faster in low- and middle-income countries than in high-income countries [13]. The highest prevalence rates are currently in the Eastern Mediterranean and Middle East with North and South America close behind. There is however considerable variation between IDF regions and within each region. For example, in the Western Pacific, the tiny island of Nauru has a comparative prevalence in 2007 of 30.7%, whilst nearby Tonga has less than half that rate at12.9%, the Philippines 7.6% and China 4.1%. In Europe, comparative prevalence rates vary from 1.6% in Iceland to 7.9% in Germany, Austria and Switzerland. The UK prevalence rate is 2.9% (age adjusted) and 4.0% (absolute), increasing to 3.5% and 4.6% respectively by 2025 [6].

In absolute numbers, 537 million adults (20-79 years) are living with diabetes mellitus globally - 1 in 10. This number is predicted to rise to 643 million by 2030 and 783 million by 2045 [43]. Alarming, it is believed that there are almost as many as such numbers with undiagnosed diabetes mellitus. Age-adjusted prevalence is set to rise from 9.3 to 10.9% in 2045 worldwide. The numbers of those with impaired glucose tolerance are equally startling with a prevalence of 7.5% in 2019, projected to rise to 8.6% in 2045 [43]. The relative proportions of type 1 to type 2 vary from 15%; 85% for Western populations to 5%; 95% in developing countries. A key demographic change to the rising prevalence of diabetes mellitus worldwide is an increasing proportion of people >65 years of age [42].

Type 2 diabetes mellitus (T2DM) is a chronic metabolic disorder afflicting millions worldwide. It is a significant global health concern with a steadily increasing prevalence [55]. The global incidence of diabetes mellitus is on the increase, more markedly in developing nations. It is no longer a condition that predominates in wealthy countries like it used to be in the past [80]. In the 21st century, it is one common disease coming to light as a disease of public health concern worldwide [22]. More than 3 in 4 adults in low and middle income nations live with diabetes [22], in Africa, 1 in every 22 adults are living with diabetes consisting of 24 million individuals of the African population [22]. This number is projected to increase to 55 million (by 129%) by the year 2045 [22].

Literature search showed that there are few data available on the prevalence of T2DM 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 settings, and affecting both gender equally [53, 55]. Poverty, social inequality, and limited access to quality healthcare have exacerbated the diabetes mellitus epidemic in Africa. Through the middle of the 1980s, diabetes mellitus was considered rare in sub-Saharan Africa, with reported prevalence rates in several countries reportedly less than 1% [48]. Africa has since experienced a six-fold increase in DM cases, rising from 4 million cases in 1980 to 25 million cases in 2014.

In sub-Saharan Africa, swift transformations in socio-demographic, cultural and economic factors propel the increasing prevalence and risk factors of diabetes and other non-communicable diseases [5]. Various hereditary, metabolic lifestyle and some other human factors play a role in the pathogenesis of type 2 diabetes mellitus [32]. A lack of exercise is believed to cause 7% of cases of type 2 diabetes mellitus [32]. Smokers are 30-40% more likely to develop type 2 diabetes mellitus than non-smokers [32]. Other human factors such as increasing age, female gender, certain medications and disease conditions also play a minor role [32].

Risk factors for type 2 diabetes mellitus are diverse. Some are modifiable, and others are not. Modifiable risk factors include overweight/obesity (increased body mass index - BMI) [57], lack of exercise or physical inactivity [6, 8], poor nutrition, smoking, and alcohol use, among others appear to be the primary culprits [32, 62]. Non-modifiable risk factors for type 2 diabetes mellitus include age [10], ethnicity/race [15], family history (genetic predisposition) [6], history of gestational diabetes, and low birth weight [32].

Unlike type 1 diabetes mellitus [16], type 2 diabetes mellitus usually develops as a result of interactions of metabolic and genetic factors. History of diabetes mellitus in the family, gestational diabetes mellitus in any previous pregnancies and ethnicity interact with advanced age, obesity and overweight, poor diet, sedentary lifestyle and smoking to raise the risk of diabetes mellitus in individuals [80]. In type 2 diabetes mellitus, the strongest risk factor both in terms of greatest relative risk and clear evidence is being overweight and this is mostly as a result of unhealthy diet and sedentary lifestyle [19]. It is estimated that physical inactivity together with being overweight caused a large percentage of the global burden of diabetes mellitus [19]. Even though, it may vary from population to population, there is also an increased risk of type 2 diabetes mellitus in people with an increased body mass index or waist circumference [60], for instance patients from south-east Asia developed diabetes mellitus at a much lower body mass index when compared to people of European descent [58].

Furthermore, several unhealthy nutritional practices have been described to cause excessive weight gain, hence increasing the risk of type 2 diabetes mellitus. These include excessive consumption of saturated fatty acids, insufficient dietary fiber intake and excessive consumption of fat in diet [80]. Sweetened beverages produced with enormous amount of free sugars worsen the risk of obesity when consumed in excessive quantities, and this risk is particularly high in children [64, 82] with recent researches suggesting an association of excessive intake of sugar-sweetened beverages with increase in the risk of type 2 diabetes mellitus [41, 47, 51, 65]. Dietary intake in early childhood increases the risk of type 2 diabetes mellitus in later stages of life. The factors that seem to increase this risk include poor development of the fetus, infants weighing less
Diabetes mellitus is a heterogeneous, polygenic disorder [27], and the responsible genes have been identified in selected subtypes of the disease. T2DM is characterized by insulin insensitivity as a result of insulin resistance, declining insulin production, and eventual pancreatic beta-cell failure [26, 30]. This leads to a decrease in glucose transport into the liver, muscle cells, and fat cells. There is an increase in the breakdown of fats with hyperglycemia. The involvement of impaired alpha-cell function has recently been recognized in the pathophysiology of type 2 DM [35, 55].

Polydipsia, polyuria and weight loss that may be accompanied by polyphagia and blurred vision are common symptoms of pronounced hyperglycemia. Patients with diabetes mellitus most commonly present with increased thirst, increased urination, lack of energy and fatigue, bacterial and fungal infections, and delayed wound healing. Type 2 DM may present in one of 4 ways: Classical symptoms, Incidental diagnosis, Acute complications notably hyperglycemic hyperosmolar state, and Chronic complications. Classical symptoms of T2DM that may be seen at diagnosis are polydipsia, polyuria, polyphagia, fungal infections (especially genital candidiasis), etc. Type 2 DM may be an incidental finding - incidental diagnosis [9].

Diabetes mellitus can be diagnosed either by glycated hemoglobin (HbA1C) criterion or plasma glucose concentration (fasting or 2-hour postprandial plasma glucose). Patients with HbA1C greater than 6.5% (48mmol/L) are diagnosed as having DM. HbA1C test gives an average of blood glucose control over the last 3 months [70]. Fasting plasma glucose (FPG) levels of more than 126mg/dL (7.0mmol/L) is consistent with the diagnosis. The two-hour Oral Glucose Tolerance Test (OGTT) is a test in which plasma glucose is measured before and 2 hours after the ingestion of 75g of glucose. DM is diagnosed if the plasma glucose (PG) level in the 2-hour sample is more than 200mg/dL (11.1mmol/L).

The World Health Organisation (WHO) and the American Diabetes Association (ADA) use a fasting plasma glucose (FPG) of 7.0mmol/L or higher to define diabetes mellitus. This originates from epidemiological studies in the 1990s which appeared to show that the risk of microvascular complications (e.g. retinopathy) increases sharply at a FPG threshold of 7.0mmol/L [81]. The relationship between plasma glucose and microangiopathy is likely to be continuous, thus a FPG of 7.0mmol/L is an arbitrary cut-off for defining diabetes which may be lowered in the future [44]. FPG, 2-h PG after 75g OGTT, and HbA1C are equally appropriate for diagnostic testing. It should be noted that the tests do not necessarily detect diabetes mellitus in the same individuals. The concordance between the FPG and 2-h PG tests is imperfect. The overlap depends on the ethnic and geographical population, and on other characteristics such as age and body mass index [2, 61].

Numerous studies have confirmed that compared with FPG and HbA1C cut-off points, the 2-h PG value diagnoses more people with diabetes mellitus. Glycated hemoglobin (HbA1C) has been accepted as the most reliable and accurate test for establishing the diagnosis as well as for evaluating glycemic control in diabetic patients. When using HbA1C to diagnose diabetes mellitus, it is important to recognize that HbA1C is an indirect measure of average blood glucose levels and to take other factors into consideration that may impact hemoglobin glycation independently of glycemia such as age, ethnicity/race, and anemia/hemoglobinopathies [63].
Monitoring progress in diabetes mellitus prevention and control is very important to strengthening appropriate surveillance mechanisms by conducting periodic population-level surveys that include measurement of risk factors and blood glucose [78]. For all cases of diabetes mellitus, the cornerstone of therapy is a combination of lifestyle modifications (diet and exercise) and pharmacotherapy (when applicable). A diet low in saturated fat, refined carbohydrates, high fructose corn syrup, and high in fiber and monounsaturated fats needs to be encouraged. Aerobic exercise for duration of 90 to 150 minutes per week is also beneficial. The major target in T2DM patients, who are obese, is weight loss [14, 45].

For patients with type 1 DM, a regime of basal-bolus insulin is the mainstay of therapy. Also, insulin pump therapy is a reasonable choice. In patients with type 2 DM whereby adequate glycemia cannot be achieved, metformin is the first-line therapy. Following metformin, many other therapies such as oral sulfonylureas, dipeptidyl peptidase-4 (DPP-4) inhibitors, Glucagon-like peptide-1 (GLP-1) receptor agonists [25], Sodium-glucose linked transporter-2 (SGLT2) inhibitors [26, 29, 37, 74, 75], thiazolidinediones e.g. pioglitazone, especially if the patient has fatty liver disease, alpha-glucosidase inhibitors e.g. acarbose; and insulin, are available.

The starting points and mainstays of treatment for type 2 diabetes mellitus are diet and lifestyle modifications such as increasing exercise and stopping smoking. The major aims are to reduce the weight of obese patients and improve glycemic control, but also to reduce risk factors for cardiovascular disease (CVD), such as hyperlipidemia [28, 31] and hypertension [36, 39], which account for 70–80% of deaths in type 2 diabetes mellitus [6]. In addition to the diet and lifestyle modifications, drugs are also used in the management of T2DM. These drugs include biguanides (sensitizers) e.g. metformin; sulfonylureas (secretagogues) e.g. glimepiride, glibenclamide; thiazolidinediones e.g. pioglitazone and the newer classes of drugs. These are summarized in Table 1 below.

**Table 1: Glucose-lowering medications**

<table>
<thead>
<tr>
<th>Class (example)</th>
<th>HbA1C reduction</th>
<th>Weight effect</th>
<th>Adverse effects</th>
<th>CVS benefit</th>
<th>Renal benefit</th>
</tr>
</thead>
<tbody>
<tr>
<td>Biguanides (e.g. metformin)</td>
<td>0.8–1.0%</td>
<td>Neutral</td>
<td>Lactic acidosis, GI</td>
<td>Yes</td>
<td>N/A</td>
</tr>
<tr>
<td>Sulfonylureas (e.g. glimepiride, etc)</td>
<td>0.8–2.0%</td>
<td>↑</td>
<td>Hypoglycemia</td>
<td>N/A</td>
<td>N/A</td>
</tr>
<tr>
<td>Thiazolidinediones (e.g. pioglitazone)</td>
<td>0.6–1.5%</td>
<td>↑</td>
<td>Edema, fractures (rare), bladder cancer (rare)</td>
<td>Yes</td>
<td>N/A</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Drug</th>
<th>Effect</th>
<th>Glucose-lowering effect</th>
<th>CVS benefit</th>
<th>Renal benefit</th>
</tr>
</thead>
<tbody>
<tr>
<td>DPP-4 inhibitor (e.g. vildagliptin)</td>
<td>0.40%</td>
<td>Neut}ral</td>
<td>Pancreatitis (rare)</td>
<td>No</td>
</tr>
<tr>
<td>SGLT-2 inhibitor (e.g. dapagliflozin</td>
<td>0.4–0.8%</td>
<td>↓</td>
<td>Genitourinary infections</td>
<td>Yes</td>
</tr>
<tr>
<td>GLP-1 receptor Agonist (e.g. liraglutide)</td>
<td>0.5–1.8%</td>
<td>↓</td>
<td>GI</td>
<td>Yes</td>
</tr>
</tbody>
</table>


Current guidelines regarding glucose-lowering medications states that diet and exercise are sufficient to achieve adequate glycemic control in <10% of type 2 DM patients. When control worsens, an oral hypoglycemic agent is generally introduced. Metformin is the recommended initial glucose-lowering medication for most patients with T2DM. If the individualized HbA1C target is not reached with metformin alone, then a 2nd line glucose-lowering agent should be added [56]. Factors to consider when choosing which agent should be used include drug efficacy, costs, side effects, patient preference, and comorbidities.

Current NICE guidelines (published in 2015) recommend the addition of a DPP-4 inhibitor, or sulfonylurea, or pioglitazone as 2nd line therapy. In contrast, the ADA/European Association for the Study of Diabetes (EASD) consensus statement (published in 2018) recommended that medications with proven benefits in CVD, heart failure, and renal protection should be prioritized for at-risk patients. This is based on recently published cardiovascular outcome trials (CVOTs) which have demonstrated that specific SGLT-2 inhibitors and GLP-1 receptor agonists substantially improve cardiovascular outcomes, heart failure, and slow down the progression of renal disease [23, 25, 26, 29, 30, 46, 56, 74, 75, 76].

Less commonly used glucose-lowering agents are other less encountered glucose-lowering agents such as α-glucosidase inhibitors (e.g. acarbose) and prandial insulin secretagogues (e.g. raproglide, nateglinide) [56]. The majority of people with T2DM will require insulin injections at some point in their lives. Various insulin formulations are available, which differ in terms of onset and duration of action and the risk of hypoglycemia. Insulin is highly efficacious and can be used to achieve almost any glycemic target if not limited by hypoglycemia. The main disadvantages of insulin, compared with other glucose-lowering therapies, are hypoglycemia, weight gain, and the need for glucose monitoring. Successful use of insulin therapy is highly dependent on appropriate patient selection, provision of adequate patient training and support, and frequent review and dose titration to safe glucose targets [52].

Persistent hyperglycemia in uncontrolled diabetes mellitus can cause several complications, both acute and chronic. Diabetes mellitus is one of the leading causes of cardiovascular disease (CVD), blindness, kidney failure [38, 71, 72], and amputation of lower limbs. Acute complications include hypoglycaemia and
diabetic ketoacidosis for type 1 DM; and hypoglycemia, hyperglycemic hyperosmolar state and hyperglycemic lactic acidotic coma for type 2 DM. Chronic microvascular complications are nephropathy [30, 33, 34], neuropathy, and retinopathy, whereas chronic macrovascular complications are coronary artery disease (CAD), peripheral artery disease (PAD), and cerebrovascular disease (CVD). It is estimated that every year, 1.4 to 4.7% of middle-aged people with diabetes mellitus have a CVD event [4].

Chronic hyperglycemia in synergy with the other metabolic aberrations in patients with diabetes mellitus can cause damage to various organ systems, leading to the development of disabling and life-threatening health complications, most prominent of which are microvascular (retinopathy, nephropathy, and neuropathy) [24, 30] and macrovascular complications leading to a 2-fold to 4-fold increased risk of cardiovascular diseases [20, 40, 73]. Poor growth and increased susceptibility to some infections may follow chronic uncontrolled hyperglycemia. Diabetic ketoacidosis or non-ketotic hyperosmolar syndrome are two acute consequences of uncontrolled diabetes that may be life threatening [1]. An abundance of microvascular and macrovascular complications present as a sequel to untreated diabetes. These complications can affect many bodily systems [5]. Moreover, diabetes mellitus bears close association with some other diseases such as hypercholesterolemia and hypertension that affect cardiovascular health. Their interactions may also increase the risk of unfavourable outcomes in people suffering from diabetes mellitus [5].

It is important to recognize that all diabetic patients are at risk of complications and type 2 DM may present with complications. Acute complications of type 2 DM include hyperglycemic hyperosmolar state (HHS), also known as hyperosmolar non-ketotic state (HONKS) which is an acute, severe disorder primarily seen in T2DM. It is associated with absolute or relative insulin deficiency, volume depletion, and acid-base abnormalities with potentially serious complications if not promptly diagnosed and carefully treated [9]. In addition, a debilitating condition (prior stroke or dementia) or social situation that compromises water intake usually contributes to the development of the disorder [49]. The other less encountered acute complication for T2DM is lactic acidotic coma. Most of the morbidity and mortality associated with type 2 DM is attributable to the chronic complications. Due to its complications, DM causes an enormous national burden with respect to morbidity. Diabetes-related chronic complications can be divided into vascular and non-vascular complications and are similar for type 1 and type 2 DM. The vascular complications of DM are further subdivided into microvascular (retinopathy, neuropathy, nephropathy), and macrovascular complications (coronary artery disease (CAD), peripheral arterial disease (PAD), cerebrovascular disease (CVD)). Microvascular complications are diabetes specific, whereas macrovascular complications have additional pathophysiologic features that are shared with the general population. Non-vascular complications include infections, skin changes, hearing loss, and increased risk of dementia and impaired cognitive function [9].

Diabetic retinopathy is the leading cause of blindness in adults aged 20 through 74 years [17] and diabetic kidney disease accounts for 40% of all new cases of end-stage renal disease [60]. Diabetes is the leading cause of non-traumatic lower extremity amputation [59]. Heart disease and strokes occur 2 to 4 times more frequently in adults with diabetes than in those who are healthy [30, 40]. Diabetic retinopathy [9], diabetic nephropathy [24, 38, 54, 72], diabetic neuropathy [66], coronary artery disease [21], diabetic foot [9] are some common chronic complications of DM.

The management of diabetes and related complications is seriously hindered by substandard care [7]. To essentially prevent, manage and control diabetes mellitus, it is imperative to understand the different aspects of the disease [18]. Yet, numerous studies have persistently shown poor understanding of diabetes mellitus among the population at large [18]. The standard of health care is increasingly being measured by patient-focused medical care assessment [3]. Many qualitative and quantitative methods are available for this patient-based assessment of care; nonetheless, patient satisfaction questionnaires are more commonly used [3].

The DCCT phase demonstrated that improvement of glycemic control reduced non-proliferative and proliferative retinopathy (47% reduction), albuminuria (39% reduction), clinical nephropathy (54% reduction), and neuropathy (60% reduction). Improved glycemic control also slowed the progression of early diabetic complications [12]. In clinical practice, intervention techniques for diabetic macrovascular disease are often disappointing because of the severity and widespread nature of the atherosclerotic vascular disease. The early diagnosis of type 2 DM is therefore very important [63]. Recent guidelines have stressed the importance of strict glucose, blood pressure and lipid control in type 2 diabetic subjects [63]. This morbidity and premature mortality is putting increased pressure on health care resources [8]. The UK Prospective Diabetes Study (UKPDS) has shown that in type 2 DM subjects, good blood glucose control [66] and tight blood pressure control [67] can prevent complications or delay their progression. The early detection of retinopathy, nephropathy and neuropathy can lead to a reduction in the incidence of blindness, kidney failure and amputation due to diabetes mellitus.

Recent studies have challenged the long-held belief that T2DM is a permanent and chronically progressive condition. Significant weight loss can normalize blood glucose levels and lead to remission of T2DM. Remission rates are highest in people with a short duration of T2DM, before the development of irreversible damage to the pancreatic β-cells. Almost 50% of participants on a very low-calorie diet (~800kcal/day for 3–5 months) in the Diabetes Remission Clinical Trial (DiRECT) attained diabetes remission after 1 year. Importantly, this trial demonstrated that diabetes remission is a practical target in 1° care. Even higher diabetes remission rates are seen after bariatric surgery. An individual who has achieved diabetes remission, regardless of the method used, will need ongoing support to prevent weight gain and thereby minimize the risk
of relapse of T2DM. It is unknown what effect diabetes remission has on the development or progression of diabetes-related complications, and so it is important that these individuals are recalled for annual review, including retinal screening [56].

Conclusion
There is a pressing need to improve access to accurate information with regards to type 2 diabetes mellitus and the quality of management of type 2 diabetes mellitus, particularly in low- and middle-income countries through well-designed and maintained diabetes mellitus registries. Such data are essential for a better understanding of the disease burden and moreover, for ensuring a better planning and provision of appropriate medical care for patients with type 2 diabetes mellitus.

Prospects for further research
Prospects for further research include to review reasons for poor glycemic control in type 2 diabetes mellitus patients with low socio-economic status, and to review the available effective treatment options for type 2 diabetes mellitus in comorbid states.

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Conflict of Interest
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