1 Introduction

1.1 Diabetes mellitus (DM)

Diabetes mellitus is a group of metabolic disorder commonly characterized by chronic hyperglycaemia accompanied by disturbance in carbohydrates, lipids and proteins metabolism.[1] Hyperglycaemia is a consequence of the defects in insulin secretion, insulin action, or both. It is elicited by inherited and/or acquired deficiency in production of insulin by the *β* -cells of the pancreas, or due to ineffectiveness of the insulin produced by the pancreatic *β*-cells. Such a deficiency/ineffectiveness results in an increased blood glucose level. If increase in blood glucose level is left undiagnosed and untreated, it can lead to complications, which can damage many of the body's systems, in particular the blood vessels and the nerves.[2, 3]

1.1.1 Prevalence of diabetes

The ever-growing prevalence of diabetes is one of the major cause of death worldwide in this century after heart diseases and cancer. In 2019, 463 million people are estimated to be living with diabetes, representing 9.3% of the global adult population (20–79 years). This number is expected to increase to 578 million (10.2%) in 2030 and 700 million (10.9%) in 2045.[4] The prevalence of diabetes in women in 2019 is estimated to be 9.0%, and 9.6% in men (given by age group in **Figure. 1**).[4]

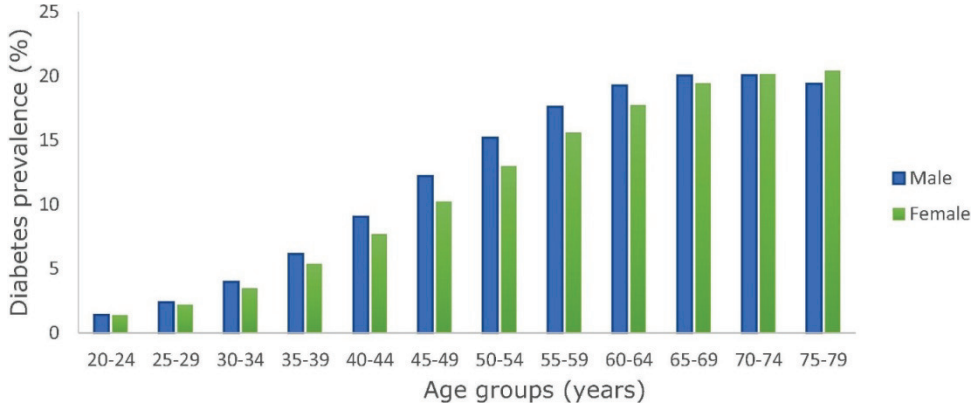

Figure 1: Diabetes prevalence by age sex in 2019**.**

The increase of diabetes prevalence with aging, leads to a prevalence of 19.9% (111.2 million) in people aged 65–79 years. It was estimated that nearly half of all people

(49.7%) living with diabetes are undiagnosed. The phase of change in diabetes popularity in many countries and regions has been boost up by rapid urbanization and dramatic changes towards inactive standard of living.[5] A considerable increase in the diabetic patients will take place in developing countries and it will be due to population growth, ageing, unhealthy diet, obesity and sedentary lifestyles.[3] By 2025, while most people with diabetes in developed countries will be aged 65 years or more, in developing countries most will be in the 45-64 year age and will be affecting their most productive years.[6]

1.1.2 Classification of diabetes mellitus

Type 1 diabetes mellitus (T1DM): T1DM which is also termed as insulin dependent diabetes mellitus (IDDM) constitutes 5-10% of individuals.[7] The disease may also affect people of any age, but commonly develops in children or young adults, hence, it is also known as juvenile-onset diabetes.[3] T1DM occurs when pancreatic *β* -cells are destroyed due to autoimmune disorder affecting considerable depletion in insulin secretion.[8] T1DM patient are characterized by less or no insulin secretion. Hence, they require daily insulin injection to control the level of blood glucose.[3] T1DM are also susceptible to additional autoimmune syndromes such as autoimmune hepatitis, Addison's disease, Graves's disease, Hashimoto's thyroiditis, celiac sprue, myasthenia gravis, and pernicious anaemia and vitiligo.[9]

Type 2 diabetes mellitus (T2DM): Type 2 diabetes mellitus or T2DM is also called non-insulin dependent diabetes (NIDDM) or adult-onset diabetes and comprises 90-95% of all cases of diabetes.[10] T2DM may remain unnoticed for many years and the diagnosis is frequently made when a complication appears or a routine blood or urine glucose test is done. It is characterized by insulin resistance and excessive insulin secretion, either or both of which may be present at the time diabetes is diagnosed.[3] The elevated occurrence of T2DM in adolescence is mostly owing to the change in lifestyle of the youngsters in terms of more inactive life and consumption of unhealthy food. Obesity is the major reason behind insulin resistance, which is mainly responsible for T2DM.[11-13] People with T2DM can often initially manage their ailment through daily regular exercise and diet. Nevertheless, over time, most individuals with T2DM will

require oral drugs and or insulin treatment.[3] The sign and symptoms of T1DM and T2DM are given in **Table 1** (next page).

Table 1: Symptoms of type 1 and type 2 diabetes mellitus

T1DM	T2DM
Abnormal thirst and dry mouth	Excessive thirst and dry mouth
Frequent urination	Frequent and abnormal urination
Lack of energy fatigue	Lack of energy and extreme tiredness
Constant hunger	Tingling or numbness of hand and feet
Sudden weight loss	Recurrent fungal infection on the skin
Bed wetting	Slow healing wounds
Blurred vision	Blurred vision

Source: https://www.idf.org/aboutdiabetes/what-is-diabetes/types of diabetes.html

Gestational Diabetes Mellitus (GDM): This form of diabetes occurs in females during second or third trimester of gestation.[14] Later in life, mothers with GDM and children born to GDM mothers have high possibility of being diabetic.[10] To prevent GDM, diagnosing using oral glucose tolerance test is thus suggested during early pregnancy for females with an increased risk of developing GDM, and in all other female during gestation between the 24th and 28th week.[15] Personal history of GDM, obesity, sedentary life, polycystic ovary syndrome, maternal age, family history of diabetes and exposure to toxin are potential factors for the development of GDM.[16]

Other specific type (monogenic diabetes): Maturity onset diabetes of the young (MODY) is considered as the most common monogenic type of diabetes, almost 1- 2% of all diabetes diagnosed are suffering from MODY.[17] Monogenic diabetes is caused due to genetic defect in some genes in the *β*-cells of the pancreas; which marks in genetic defects of *β*-cells job, along with deficiencies of insulin action or a decrease in the amount of *β*-cells; individuals with ailments of the exocrine pancreas, such as pancreatitis or cystic fibrosis; individuals with dysfunction related with other

endocrinopathies (e.g. acromegaly) and persons with pancreatic dysfunction affected by drugs, infections or chemicals.[10, 14]

1.1.3 Pathophysiology of Type-2 diabetes mellitus:

Type 2 diabetes mellitus (T2DM) is a complex and progressive disease characterized by various metabolic defects and is affecting multiple organs like pancreas, liver, gut, muscle and adipocytes (**Figure 2**).[18-21]

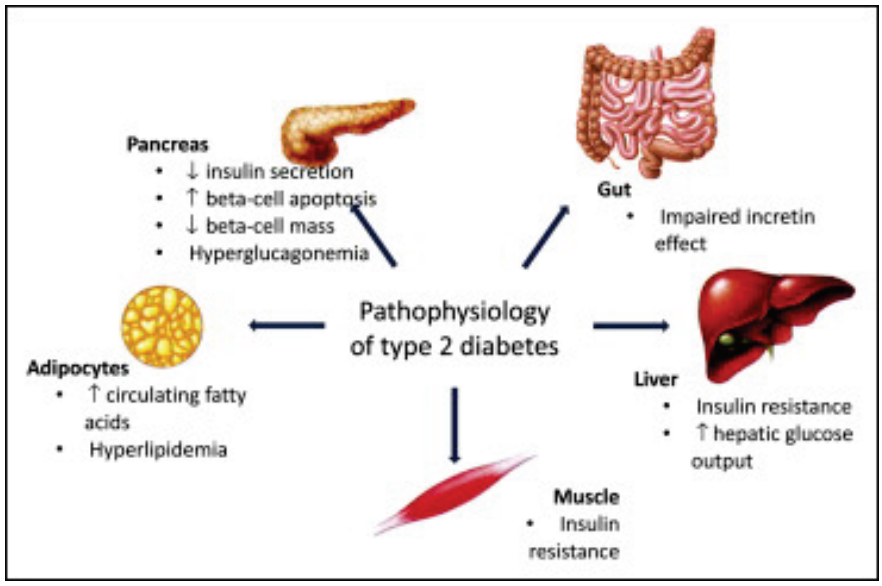

Figure 2: Pathogenesis of type-2 diabetes mellitus

The main defects contributing to the development of type 2 diabetes are impaired insulin secretion and insulin resistance in peripheral tissues, such as adipose, muscle, and liver (**Figure 3**).

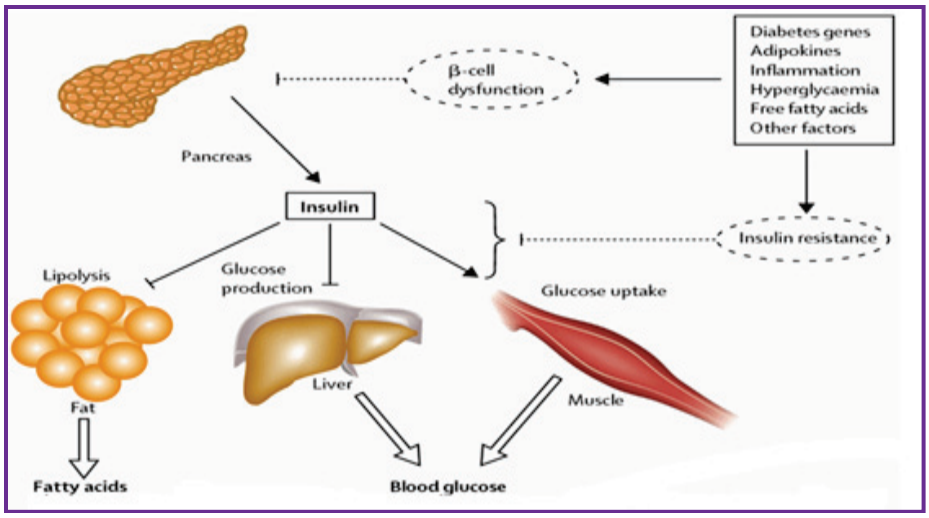

Figure 3: Effect of insulin deficiency and insulin resistance in T2DM

The decrease in insulin secretion is due to the gradual decline in pancreatic beta-cell function and also is linked to reduced beta-cell mass, which is evident before the onset of frank type 2 diabetes.[17,22] Indeed, some data suggest that, at the time of diagnosis, a mere 20% of *β*-cell function remains active.[23] The development of chronic hyperglycaemia further impairs *β*-cell function and insulin secretion. In addition, increased hepatic glucose production, due to both impaired insulin action on the liver and excessive glucagon secretion and an impaired incretin effect play a major role in the pathophysiology of T2DM.[18, 24, 25]

The hormones glucagon-like peptide 1 (GLP-1) and glucose-dependent insulinotropic polypeptide (GIP) are responsible for the incretin effect, a phenomenon whereby insulin secretion increases more in response to an oral compared with an intravenous glucose challenge.[25, 26] GLP-1 has been shown to regulate beta-cell mass by inhibiting beta-cell apoptosis *in-vitro* and in animal models [27],[28] and improve *β*-cell function in patients with type 2 diabetes.[29] However, the incretin effect is impaired in patients with T2DM, mainly due to loss of the insulinotropic effect of GIP and GLP-1 in some, but not all patients.[30]

Genetics: Epidemiologic and genetic studies suggest a strong genetic basis for development of type-2 diabetes. (~90% concordance rate in monozygotic twins). However, genes that account for the majority of cases have not yet been identified. Type-2 diabetes appears to be a genetically heterogeneous disorder and different

genes may be implicated in different populations. Rare monogenetic defects in insulin secretion or synthesis are:

- Mutant insulin gene (which results in dysfunctional insulin)
- Abnormal processing of pro-insulin
- Defects in glucose-mediated insulin secretion by the pancreatic *β*-cell. These autosomal dominant conditions are known as Maturity Onset Diabetes of the Young (MODY) syndromes. The following genetic defects may be involved:
  - **MODY1** - Mutant transcription factor, Hepatic Nuclear Factor-4 alpha (HNF-4a)
  - **MODY2** - Impaired *β*-cell Glucokinase activity
  - **MODY3** - Hepatocyte Nuclear Factor 1A (HNF-1a)
  - **MODY4** – Insulin Promoter Factor-1 (IPF-1) (necessary for normal *β* cell development and functioning).

Environment: Despite its strong genetic basis, the rising incidences of T2DM over the past few decades strongly suggest that important environmental contributions to its pathogenesis exist. Environmental factors play a key role in both types of diabetes. Common environmental factors are associated with type 1 and type 2 diabetes, including dietary factors, endocrine disruptors, other environmental polluters and gut microbiome composition. In addition to well-established roles in type 2 diabetes, obesity and insulin resistance may be accelerators of type 1 diabetes. Conversely, islet autoimmunity associated with possible environmental triggers (e.g., diet, infection) may have a role in a subset of people diagnosed with type 2 diabetes. A manipulation of lifestyle provides an opportunity to reverse the diabetes trend. Stated another way, we cannot change our genetic make-up, but we can alter environmental factors. Indeed, many studies have shown that diet and exercise slow the onset of diabetes in persons with impaired glucose tolerance (IGT).[31-33] Also, low glycaemic index diets have been shown to promote weight loss along with having metabolic benefits in persons with type 2 diabetes.[34] The difficulty, of course, is to get people to change their habits.

Insulin deficiency and insulin resistance: Although insulin resistance may be thought as the central defect in the pathogenesis of T2DM, and most patients with the disease have insulin resistance, it is the health of the *β*-islet cells that determines the development of hyperglycaemia, which defines clinical diabetes. This concept is supported by data from the UK Prospective Diabetes Study showing that in patients with T2DM, *β* - islet cell function is reduced by approximately 50%. The importance of the *β* islet cell dysfunction in the pathogenesis of diabetes is further highlighted by the fact that insulin resistance is highly prevalent in the U.S. (approximately 25% of the population) but only 7% of the population has clinical diabetes.[35]

1.1.4 Diagnosis of diabetes mellitus

The clinical diagnosis of diabetes mellitus depend on any one of the mentioned plasma glucose standards with >126 mg/dL of fasting plasma glucose, 2 h plasma glucose with >200 mg/dL during a 75-g oral glucose tolerance test (OGTT), and a random plasma glucose with >200 mg/dL with classic signs and symptoms of hyperglycaemia or haemoglobin A1C level >6.5%.[36]

1.1.5 Complications of diabetes mellitus

Diabetes mellitus is also associated with different complications if left undiagnosed and untreated as shown in **Figure 4**.[37] The types of complications are mentioned below:

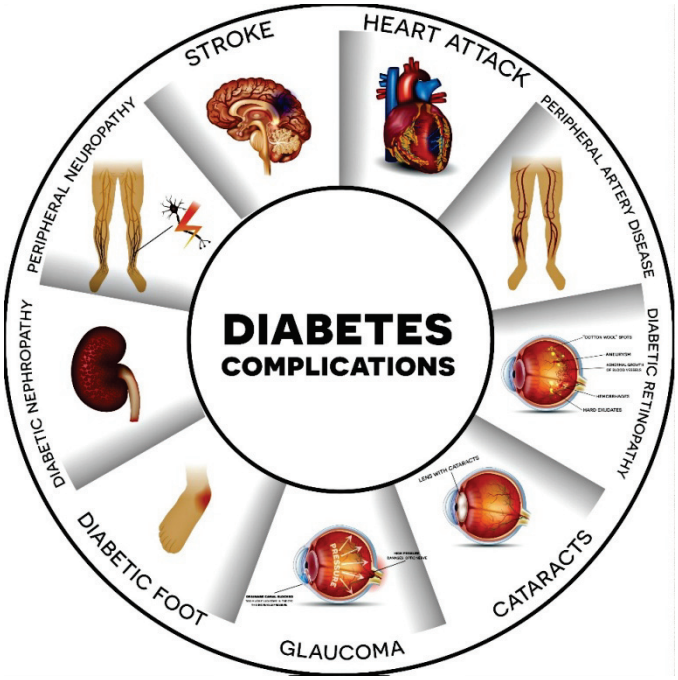

Figure 4: Diabetic complications resulting due to chronic hyperglycaemia

Source: https://www.umassmed.edu/dcoe/diabetes-education/complications/

(i) Micro-vascular complications: Diabetic retinopathy is commonly identified by features such as retina lesions and it is a complication that largely contribute to most of the cases of blindness among adults aged 20-74 years.[38, 39] In the initial stages of diabetic retinopathy, high blood glucose level can cause intramural pericyte loss and thickening on the basement membrane, which adds to alterations in the vascular porousness, blood vessels of the retina and changing the blood-retinal barrier.[38] Diabetic neuropathy is reported to affect more than half of all individuals with diabetes.[40] Diabetic neuropathy is a major factor for spinal cord and higher central nervous system damage.[41, 42] Medically, the development of proteinuria following a failure in glomerular filtration capacity, which is found to be prevalent over an extensive duration of time, frequently over 10–20 years, can cause nephropathy.[43] Diabetic nephropathy stands as one of the major cause of end stage renal failure in western cultures.[44]

(ii) Macro-vascular complications: The main pathological process in macrovascular complication is the development of atherosclerosis, which causes tightening of the arterial walls.[45] Atherosclerosis is due to prolonged inflammation and damage to the

tissue or fibrosis.[45, 46] In connection to endothelial injury and inflammation, oxidized lipids from low density lipoprotein particles gather in the endothelial wall of the arteries.[45] Furthermore, monocytes can also penetrate the arterial wall and give rise to macrophages, which assist in accumulating the oxidized lipids to form foam cells inside the arteries.[45] Ultimately, after the formation of the foam cells, these cells can arouse the macrophage to proliferate and attract the T-lymphocytes. These T-lymphocytes can in turn stimulate the proliferation of smooth muscle that are present in the arterial walls. This process can lead to acute vascular infarction of the heart.[45]

(iii) Liver diseases: in which disorder such as abnormal liver enzymes, non-alcoholic fatty liver disease (NAFLD), cirrhosis, hepatocellular carcinoma, and acute liver failure are associated with diabetes.[47] The prevalence of diabetes in cirrhosis is 12–57%.[48, 49] Patients with diabetes have a high prevalence of liver disease and patients with liver disease have a high prevalence of diabetes.[47]

1.2 Obesity

Obesity is caused due to the imbalance between energy intake and expenditure that can subsequently lead to accumulation of excess fat.[50] It is distinct as a disease in which excess body fat has accumulated to a level that can adversely affect the health of an individual. The American Medical Association classified obesity as a disease in 2013. Reports suggest that overweight and having excess of body fats during adolescence may predict later increases in health risks and adult mortality.[51-54] Excess energy consumptions are reported to stimulate hyperinsulinemia and insulin resistance through stimulation of insulin secretion, triglyceride synthesis and fat accumulation.[55] This can result in insensitivity to insulin as fat cells are capable of hampering or obstructing the cells of insulin sensitivity.[55] The insulin resistance seen in obesity is believed to involve primarily muscles and liver, with increased adipocyte-derived free fatty acids (FFA) promoting triglyceride accumulation in these tissues.[56] Thus, circulating glucose is inhibited from metabolising and eventually result in insulin resistance and can therefore, lead to diabetes. Thus, the state of obesity predates diabetes.[57] Reports indicated that obesity, together with insulin resistance, elevated

blood pressure, impaired glucose tolerance and dyslipidemia are well known risk factors that increase the incidence of cardiovascular disease and T2DM.[58-61]

1.2.1 Prevalence of obesity

Once considered a problem only in high-income countries, overweight and obesity are now drastically on the rise in low- and middle-income countries, particularly in urban places.[3] Obesity incidences have doubled up since 1980 in more than 70 countries and constantly augmented in most other countries.[62] The number of people in 2015, affected with obesity was reported to be 107.7 million (98.7-118.4) children and 603.7 million (588.2-619.8) adults worldwide.[62] It is estimated that 2.8 million people die each year as a result of being overweight or obese, and that 35.8 million of global disability-adjusted life years (DALYs) are caused by overweight and obesity.[63, 64]

1.2.2 Diagnosis of obesity

The simple measurement of obesity is the body mass index (BMI), a person's weight (in kilograms) divided by the square of height (in meters).[65] A person having BMI of 30 or more is commonly considered obese. An individual with a BMI equal to or more than 25 is considered overweight.[3] Obesity can be also characterized by abdominal obesity, insulin resistance, dyslipidaemia such as high cholesterol level, high triglyceride level and low high-density lipoprotein (HDL), hypertension, impaired glucose tolerance, pro-inflammatory state, i.e. elevated tumor necrosis factor alpha (TNF-α), C-reactive protein (CRP) and interleukin (IL)-6 and procoagulant (elevated plasminogen activator inhibitor [PAI- 1]) levels.[66]

1.2.3 Complications of obesity

The complication of obesity includes insulin resistance, inflammation, dyslipidaemia, stroke, hypertension, cancer, heart failure, etc. as shown in **Figure 5**. In combination, obesity and diabetes can put a person at risk in developing various complication if left undiagnosed and untreated. Therefore, globally, it is considered as one of the severe health threats.[67] Studies suggest that reducing the prevalence of obesity can ultimately reduce the incidence of T2DM.[68] Obesity is reported to be associated with liver abnormalities, commonly called non-alcoholic fatty liver disease (NAFLD). It is characterized by an elevated level in intrahepatic triglyceride content (i.e. steatosis) with

or without inflammation and fibrosis (i.e. steatohepatitis).[69] Additionally, obesity is an important independent risk factor for the development and progression of chronic kidney disease.[70-72]

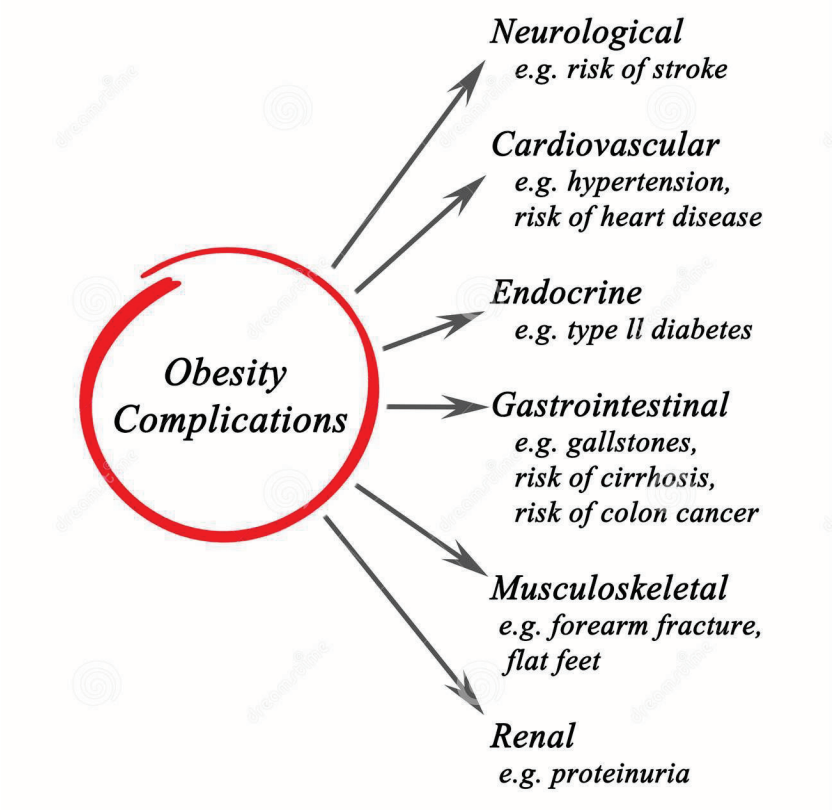

Figure 5: Illustration the complication of obesity

Source: https://www.dreamstime.com/complications-obesity-medicine-dangerous-complications-obesity-image102727746

1.3 Treatment of diabesity (diabetes and obesity)

The term diabesity was coined to express the close relationship between obesity and diabetes.[73] Both diseases are characterized by the presence of peripheral insulin resistance and pancreatic β cell insulin deficiency.[74] In 1997 it was revealed that for every kg of weight gained, the risk of diabetes increased by 4.5-9%, highlighting a potential link between obesity and Type 2 Diabetes Mellitus (T2DM).[75] Today, approximately 90% of T2DM cases are attributed to excess weight gain (WHO), confirming weight gain as a significant contributor to an increased risk of T2DM.[76] Since last decade, the prevalence of obesity (defined as having a body mass index (BMI) of >30 kg/m^2) has grown severity in all populations. Today, obesity affects more than 650

million individuals globally, and is therefore considered a worldwide epidemic (WHO). In the UK, 2 in every 3 individuals are overweight or obese (Diabetes UK) and in the US, only a third of the population is considered to have a normal BMI (Centers of Disease Control and Prevention, USA). The current predicament of obesity is attributed to a Western lifestyle, consisting of highly palatable and calorie-dense food and a reduction in energy expenditure (WHO). Obesity is associated with numerous co-morbidities, the most prevalent being T2DM.[77] T2DM is associated with a decline in β cell insulin secretion, hyperglycaemia, progressive *β*-cell apoptosis and whole-body insulin resistance, resulting in a reduction in glucose uptake in the periphery (skeletal muscle, liver and adipose tissue).[78]

The treatment of diabetes comprises of three main approaches, lifestyle intervention (diet and exercise) along with pharmacological insulin replacement therapy and the use of oral hypoglycaemic agents like sulfonylurea, biguanide, meglitinide, insulin sensitizers, dipeptidyl peptidase 4 (DPP-4) inhibitors, sodium-glucose co transporter (SGLT2) inhibitors, α-glucosidase inhibitors, insulin therapy such as Lispro, Aspart, Isophane insulin, Insulin glargine and insulin sensitizers like rosiglitazone, pioglitazone.[36]

The treatment of diabetes using these commercially available drugs are also known for their association with a number of side effects. Diet control and lifestyle modification remain the main steps in obesity management.[79, 80] The use of pharmacological agents such as appetite-suppressants, inhibiting fat absorption, and thermogenic drug are often prescribed for weight loss in treating obesity along with lifestyle changes.[81, 82] However, most of the antiobesity drugs that were approved and marketed have now been withdrawn due to serious adverse effects.[83] In 2000, the European Medicines Agency (EMA) recommended the market withdrawal of several antiobesity drugs, including phentermine, diethylpropion, and mazindol, due to an unfavorable risk to benefit ratio.[83, 84] Therefore, better drugs with potential action is need of the hour for preventing and treating metabolic disorder such as diabetes and obesity, in order to avoid the progression of the disorder to multiple complication.

1.3.1 Antidiabetic drugs

Metformin was first discovered from *Galega officinalis*, a herbaceous plant whose active compounds comprises of guanidine, galegine, and biguanide, which is found to decrease blood glucose levels.[85] Metformin is among one of the most widely recommended drug for the treatment of diabetes.[86] Metformin exerts its blood glucose lowering property by sensitizing peripheral tissues to insulin, enhancing glucose uptake, inhibiting hepatic gluconeogenesis, decreasing hyperinsulinemia and reducing protein synthesis.[85, 87, 88] Findings also suggest that metformin lower plasma lipids level through Peroxisome proliferator-activated receptor alpha (PPARα) pathway, which ultimately prevents cardiovascular diseases.[85] The thiazolidinedione (TZD) consist of PPARγ agonists, rosiglitazone and pioglitazone were approved in 1999. This class of drugs also commonly known as glitazones, unlike the biguanide metformin, these drugs are unable to increase insulin secretion but rather increase insulin sensitivity in muscle and adipose tissue and in the liver by stimulating PPARγ, which is involve in glucose and fat metabolism and affect gene regulation in the target cells.[89-91] The side effects of these agents include increased liver enzymes, weight gain, edema and mild anaemia.[92] Sulphonylureas e.g. glibenclamide, first approved in 1994, are considered as insulin secretagogues and the oldest available class of oral glucose-lowering agents.[93-95] Their mechanism of action includes insulin secretagogues and these drugs trigger insulin release via glucose-independent manner by binding to a regulatory protein called sulphonylureas receptor on the pancreatic *β*-cells. Following, binding to the receptors, they elicit closure to ATP-dependent potassium (K_{ATP}) channels, membrane depolarization and influx of calcium through voltage dependent channels, which subsequently leads to insulin secretion.[96-98] Side effects of sulphonylureas include weight gain, low blood sugar, upset stomach and skin rash or itching. Following food intake, food are broken down to simple sugar by α- glucosidase enzyme in the brush border of the small intestine. α-Glucosidase inhibitor are drugs that inhibit the digestion of carbohydrates thus, result in delay and decreased absorption of sugar. Side effects such as diarrhea, abdominal pain and flatulence are encountered while using α-glucosidase inhibitors.[99, 100] The other antidiabetic drugs include the glucagon-like peptide 1 (GLP-1) which stimulates insulin biosynthesis and excretion, inhibits glucagon

secretion, appetite suppressor, promotes the regeneration and proliferation of pancreatic *β*-cells and decelerates gastric emptying.[25, 101, 102] GLP-1 agonists are also generally associated with gastrointestinal side effects and nearly 30-45% of patients experience one or more events of diarrhea, nausea or vomiting. Another class of drugs known as dipeptidyl peptidase-4 (DPP-4) inhibitors such as Vildagliptin, function by increase in circulating GLP-1 and gastric inhibitory polypeptide **(**GIP) levels, this leads to increased glucose-dependent insulin secretion and ultimately decreased blood glucose, hemoglobin A1C and glucagon levels.[102, 103] Vildagliptin is accompanied with side effect such as nausea, peripheral edema, headache, weight gain, dizziness, upper respiratory infection, back pain and diarrhea.[104] Canagliflozin, an oral drug, reduces renal threshold for glucose reabsorption and increasing the urinary glucose excretion ending up in weight loss by selectively inhibiting sodium-glucose transporter-2 inhibitors (SGLT2) and also control normal level of blood glucose.[105] Side effect of these drugs includes genitourinary infections.[106] The summarized information on the action and side effects of the drugs is given in **Table 2**.

Table 2: Currently available anti-diabetic drugs[104, 107]

Drug	Class	Mechanism	Adverse Effect
Biguanide	Metformin	Reduces hepatic glucose production, increases peripheral glucose utilization and insulin sensitivity	Gastrointestinal complaints and lactic acidosis
Sulphonylureas	Glimepiride	Stimulates insulin release from pancreas and reduces post absorptive rates of endogenous glucose production	Very rare adverse effects compared to other sulphonylureas side effects such as hypoglycemia and weight gain
TZD	Rosiglitazone	Lowers insulin resistance in peripheral tissue by activating PPARγ	Weight gain, fluid retention and heart failure
Disaccharidase inhibitors	Acarbose	Inhibits intestinal alpha glucosidase enzymes	Gastrointestinal disturbance such as flatulence, abdominal distension, stomach rumble and diarrhea
GLP1 agonists	Liraglutide	Stimulates insulin biosynthesis and secretion, inhibits glucagon secretion and slows gastric emptying	Nausea and vomiting

DPP-4 inhibitors	Vildagliptin	Inhibits DPP-4 that improves glycemic control	Nausea, peripheral edema, weight gain, headache, dizziness, upper respiratory infection, back pain and diarrhea
SGL2 inhibitors	Canagliflozin	Inhibits SGLT2 in the kidneys	Low incidence of hypoglycemia and genital infections in females

1.3.2 Anti-obesity drugs

Food and Drug Administration (FDA) officially approved, Orlistat as an antiobesity drug for weight loss in 1998. Until now Orlistat commonly prescribed and available for the treatment of obesity.[108, 109] Crucially, Orlistat is the first gastrointestinal lipase inhibitor for the management of obesity.[110] Orlistat deactivated gastrointestinal lipase, decreasing the absorption of dietary fat.[111] Significantly, orlistat diminished fat absorption by binding covalently to the serine residue of the active site of gastric and pancreatic lipases. It was suggested that Orlistat administration with fat comprising foods partly prevented the hydrolysis of triglycerides. Hence, decreasing the consequent absorption of monoglycerides and FFA.[112] Furthermore, Orlistat improved body weight, blood pressure and serum lipids level.[113] This was observed by the ability of Orlistat to normalize total cholesterol, triglycerides, LDL and HDL. Abdominal pain, bloating, flatulence, oily stools, diarrhea and decrease absorption of fat-soluble vitamins are the side effects with respect to Orlistat. In the late 1990s, Sibutramine, a reuptake inhibitor of noradrenalin and serotonin was developed as a weight reduction drug.[114] The drug was linked to cardiovascular side effects and caused an increase in strokes and heart attacks.[115] Rimonabant well known as a cannabinoid 1 receptor (CB1) antagonist can also inhibit the process of lipolysis in the adipocytes. Rimonabant was withdrawn in 2008 since it was associated with increased incidences of depression and suicidal thoughts.[109, 116] Even though there are number of medication being used worldwide but these synthetic drugs are also linked to a number of side effects. Therefore, the search of alternatives with less or no side effects is ongoing. In **Table 3**, the summarized action and side effects of the drugs are presented.

Table 3: Available anti-obesity drugs.

Drugs	Mechanism	Adverse effect	Status
Phenterminea	Sympathomimetic Amine (appetite suppressant)	Insomnia, tremor, ↑blood pressure and pulse rate, headache, palpitation, constipation	Approved drug for short-term weight management in U.S., Korea and some countries, withdrawn on 2000 in U.K.
Diethylpropiona	Sympathomimetic Amine (appetite suppressant)	Insomnia, tremor, ↑blood pressure and pulse rate, headache, palpitation, constipation	Currently approved drug for short-term weight controlling.
Zonisamidea	Anticonvulsant agent	↑Nervousness, sweating, tremors, gastrointestinal adverse effects, hypersomnia, fatigue, and insomnia	Used off-label
Topiramatea	Anticonvulsant agent	Paraesthesia, dizziness, altered taste, fatigue, memory impairment, somnolence, anorexia and abdominal pain	Used off-label
Sibutramine	Serotonin/Noradrenalin reuptake inhibitor	Increased risk for stroke and myocardial infarction	Withdrawn in 2010
Rimonabant	CB1 receptor antagonist	Depression and anxiety	Withdrawn in 2008
Orlistat	Pancreatic lipase inhibitor	Abdominal pain, bloating, flatulence, oily stools, diarrhea, ↓ absorption of fat soluble vitamins	Only approved drug for long-term weight management
Atorvastatin	Inhibitor of HMG-CoA reductase	Liver and muscle toxicity	In used

Innovative new therapies that could improve glucose metabolism and reduce body weight and excess food intake will provide benefits to such patients. Although there are

a number of therapeutic options such as sulfonylureas, metformin, glitazones and glinides, they are unable to get satisfactory glycemic control without adverse side effects. Thus, there is an urgent need of identification of novel therapeutic approaches for the treatment of T2DM that provide a good glycemic control with a minimum or no side effects.[117, 118] Recently, GPR119 modulators have been suggested for the treatment of metabolic disorders.

1.4 GPR119 Agonists:

1.4.1 Discovery and Receptor Expression

The G protein-coupled receptor 119 (GPR119) was first identified through a bioinformatics approach and has been described as a rhodopsin-like, class A receptor.[119] The human GPR119 gene is located on the X chromosome (Xp26.1) and contains 335 amino acid residues and is shown in **Figure 6**.

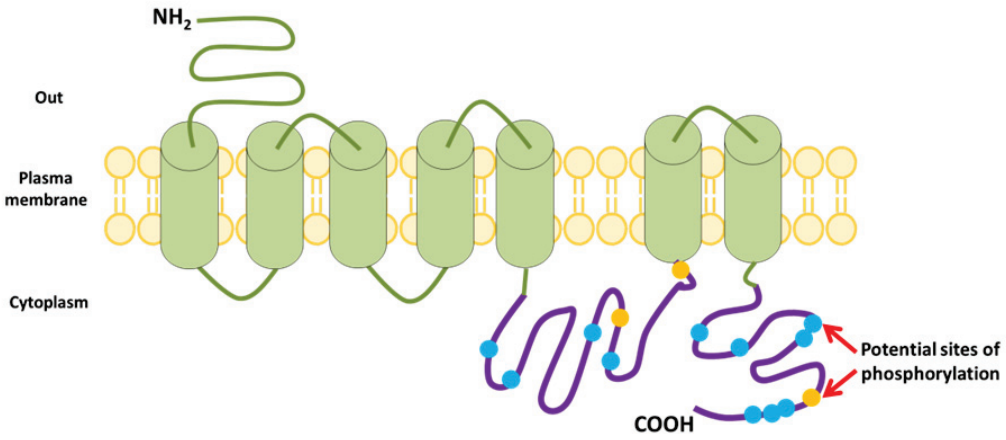

Figure 6: A topology model of the Human GPR119 membrane with their amino acid sequences. Clusters of serine (S) and threonine (T) residues are highlighted in blue orange circles in the third intracellular loop and the C-terminus domain, and could represent potential sites of phosphorylation.

This receptor has been described in the literature under various synonyms, including SNORF25,[120] RUP3,[121] GPCR2,[122] 19AJ,[123] OSGPR116[124] and glucose-dependent insulin tropic receptor.[125, 126] Based on phylogenetic analysis and sequence similarity, GPR119 belongs to the biogenic amine and MECA (Melanocortin, Endothelial differentiation gene, Cannabinoid, and Adenosine) receptor clusters. However, GPR119 shares 28% transmembrane sequence homology with Adenosine A1 and A3 receptors

whereas it does not have significant sequence similarity to GPR40/FFAR1 (18%) and GPR120/FFAR4 receptors (24%)[127] and also revealed that the mouse GPR119 shares 82.1% homology and rat GPR119 shares 73.7% homology with human GPR119.[128]

Several groups have investigated the GPR119 receptor expressions using reverse transcription–polymerase chain reaction **(**RT PCR) or hybridization analysis. GPR119 receptors were predominantly expressed in *β*-cells of pancreas and entero-endocrine (L and K) cells of intestine.[125, 129, 130] However, relatively low expression GPR119 receptor has been found in brain, liver and skeletal muscles.[126, 131-133] Interestingly, Gpr119 mRNA level in human fetal liver is very high.[120] Recently, Yang JW *et al.*[134] For the first time revealed that, GPR119 receptors were expressed in mouse hepatocytes and liver tissues. However, the expression of GPR119 in adipose tissues is unknown at present (see **Figure 7**).[135]

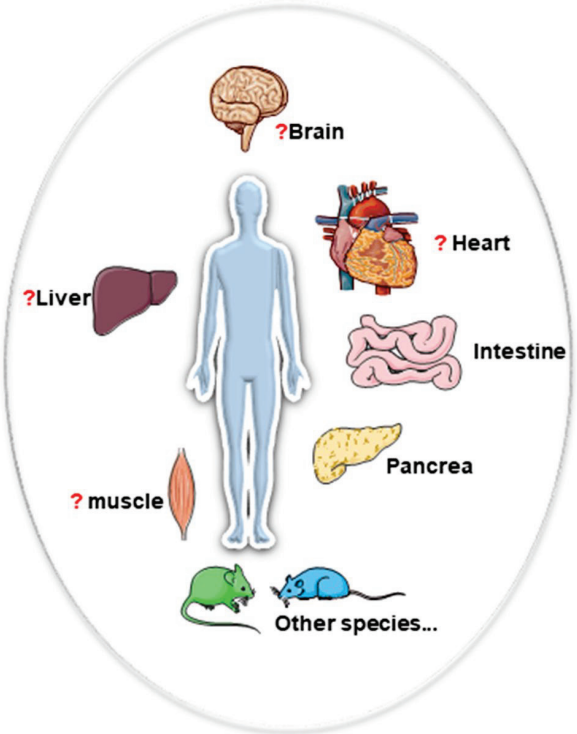

Figure 7: Tissue distribution of GPR119

GPR119 may be present in the brain, gastrointestinal digestive system, pancreas, liver, and heart, but there is still controversy (indicated with question marks in the figure). The reason may be low expression or differences in detection methods. In the future, some strict detections are still needed.

1.4.2 Signalling and Physiological Functions

GPR119 is a rhodopsin-like, class A receptor and It has been shown to predominantly couple through cyclic adenosine 3,5-monophosphate (Gαs/cAMP) pathway and leads to stimulation of adenylate cyclase.[125] Many endogenous ligands and synthetic small molecule agonists of GPR119 have been shown to increase cAMP levels. The fatty acid derivatives such as lysophosphatidylcholine (LPC), oleoylethanolamide (OEA), N-oleolydopamine (OLDA) and 2-oleoylglycerol (2-OG) have been reported as an endogenous ligands of GPR119.[131, 132, 136, 137] In *in-vitro* studies, these endogenous ligands were demonstrated to increase cAMP, enhanced glucose stimulated insulin secretion and GLP-secretion via GPR119 receptor.[129, 131, 132, 136] Notably, OLDA also improved glucose tolerance with increased GIP levels in GPR119 wild type but not in knockout mice.[136] Overall, GPR119 agonists act via a dual mechanism of action 1) activation of GPR119 receptor in pancreatic *β*-cells results in direct stimulation of glucose-dependent insulin secretion 2) activation of GPR119 in entero-endocrine cells results in stimulation of incretin release (GLP-1 & GIP), leading to improved acute glucose tolerance. However, $GPR119^{-/-}$ mice have normal islet function, body weight, and fed/fasted glucose levels.[125, 126] Moreover, there were no significant differences in body weight gain, glucose levels and insulin sensitivity when $GPR119^{+/+}$ and $GPR119^{-/-}$ mice fed on high fat diet.[137] However, GLP-1 secretion was significantly attenuated in $GPR119^{-/-}$ mice as compared to wild-type mice, suggesting that GPR119 receptors play a major role in the regulation of GLP-1 secretion.[137-139] GPR119 receptor agonists caused increase in intracellular cAMP levels in pancreatic *β*-cells and further potentiated glucose-stimulated insulin secretion (GSIS) in preclinical studies. Several GPR119 agonists have shown enhanced insulin and incretin secretion, improved glucose tolerance, inhibition of gastric emptying, suppression of feed intake, and finally body weight loss in rodent studies.[140] The pharmacological actions of GPR119 receptor agonists are depicted in **Figure 8.**[140]

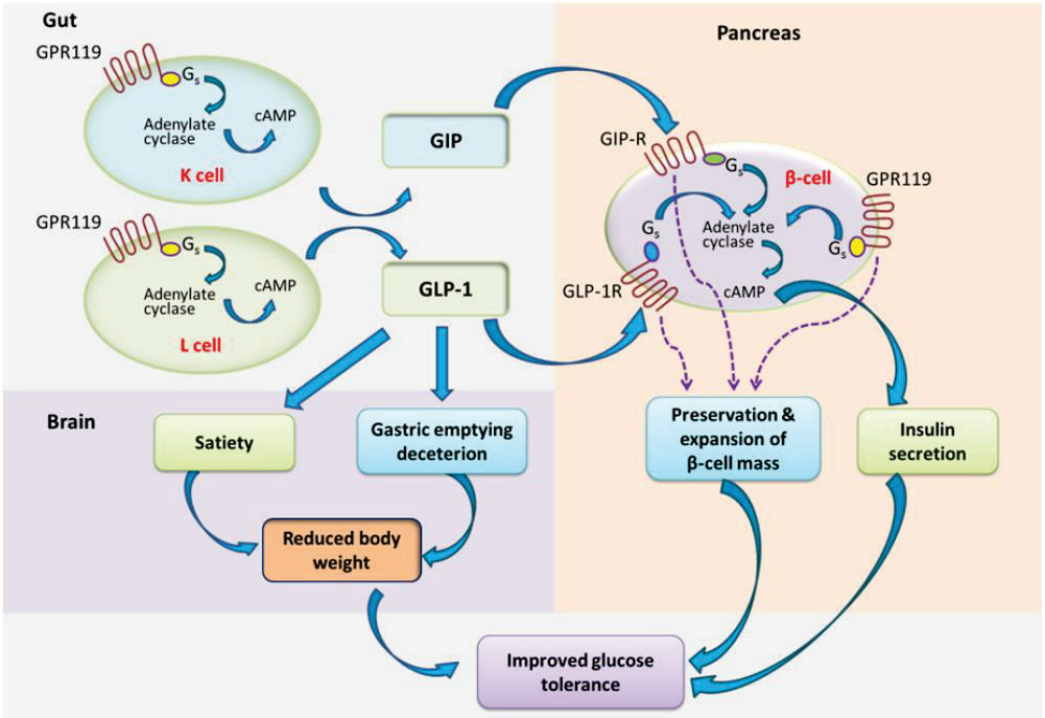

Figure 8: The possible Pharmacological actions of GPR119 agonists

GPR119 is expressed on certain enteroendocrine cells (L and K cells) in the small intestine and by β-cells within the islets of Langerhans of the pancreas. In all three-cell types, ligation of GPR119 by an agonist leads to the activation of adenylate cyclase and a rise in cAMP. This triggers the release of glucagon-like peptide 1 (GLP-1), and glucose-dependent isulinotropic peptide (GIP) or insulin from L, K and β-cells, respectively. Additionally, GLP-1 and GIP can both interact with their cognate receptors on the β-cell to elicit insulin secretion. Thus, GPR119 agonists lead to a rise in insulin release by both direct mechanisms. Since GLP-1 (and probably GIP) also promotes β-cell viability, it is possible that orally acting GPR119 agonists may influence both the secretory activity and the viability of β-cells, leading to improved glucose homeostasis in patients with T2DM.

1.4.3 GPR-119 Agonists in Anti-diabetes Therapy

AR231453, a first generation GPR119 agonist discovered by Arena Pharmaceuticals improved oral glucose tolerance, increased GSIS and also enhanced GLP-1, GIP and total peptide YY (PYY) release in mice.[126, 127] AR231453 further showed partial improvement in glucose tolerance in presence of exendin-3 (GLP-1R antagonist) suggesting that indirect actions via GLP-1 release and direct actions on pancreatic *β*-cells contribute to glucose homeostasis. Sub-chronic treatment with APD668, APD597 (JNJ-38431055) which was co-developed by Arena and Johnson & Johnson, a second generation compounds also demonstrated significant blood glucose and HbA1c reduction in male ZDF rats, $Lepr_{ob/ob}$ mice and monkeys.[141, 142] MBX2982 developed by

CymaBay Therapeutics (formerly Metabolex) and GSK1292263, a potent and specific GPR119 agonist that increased incretin levels, GSIS, improved glucose tolerance and delayed the onset of diabetes in high fat diet fed female ZDF rats.[143, 144] Furthermore, GPR 119 Agonists also caused a significant improvement in glucose tolerance and insulin secretion in rodent studies.[132, 145-148] Some of the GPR119 agonists have shown significant additive glucose lowering efficacy and synergistically enhanced GLP-1 levels in rodent studies[126, 143, 148] and also stimulated β-cell replication and GLP-1 secretion in streptozotocin induced diabetic mice.[149, 150] Similarly, PSN632408, a GPR119 agonist alone or in combination with Sitagliptin, a DPPIV inhibitor increased human *β*-cell neogenesis in human-islet-transplanted NOD-SCID mice.[151, 152] Recently, another GPR119 agonist, DA-1241 also demonstrated significant preservation of *β*-cells mass in HFD/STZ diabetic mice model. Overall, these finding suggest that GPR119 agonists improved glucose excursion via direct action on pancreatic β-cells and indirect action via incretin release partially thus contributing to improvement in glucose tolerance and the preservation of *β*-cells in rodent studies.

1.4.4 GPR-119 Agonists in Anti-obesity Therapy

Oleoylethanolamide (OEA) an endogenous ligand of GPR119 and GLP-1 whose secretion was increased by GPR119 agonist, demonstrated reduction in feed intake in rodents.[153, 154] Therefore, it is tempting to speculate that GPR119 agonists might have role in appetite suppression, in gastric emptying and in body weight loss. However, the actions of OEA could be due to activation of PPAR-α receptor and the effect on feed intake was independent of GPR119 because OEA also showed effects in both GPR119 wild type and knockout mice.[138, 155] It is very well known that GPR119 agonists stimulate GLP-1 secretion, cause inhibition of gastric empting and appetite suppression leading to body weight loss in preclinical and clinical studies.[156, 157] Based on this rationale, oral administration of PSN821 showed reduced weight gain (8.8%), fat pad weight and plasma leptin levels in diet-induced obese rats. PSN821 also caused inhibition of gastric emptying in normal rats.[132] Importantly, Chu ZL *et al.*[126] did not observe any effect on feed intake or body weight in their studies; rather compounds more potent than AR231453 showed feed intake reductions only at higher doses than those needed to reduce glucose levels. Moreover, AR231453, a prototype GPR119 agonist inhibited

gastric emptying in GLP-1 receptor$^{-/-}$, DIRKO, GLP-2 receptor$^{-/-}$ mice and even in presence of Y2 receptor antagonist in mice. In addition, AR231453 reduced gastric emptying in wild type but not in GPR119$^{-/-}$ mice.[158] All these findings suggest that AR231456 inhibited gastric emptying independent of GLP-1 receptor, GLP-2 receptor and Y2 receptor. In contrast, GSK1292263 did not demonstrate effects on gastric emptying and body weight in rodent studies.[144] However, several other GPR119 agonists such as YH18421 and AS-1269574 showed significant reduction in feed intake and body weight loss in rodent studies upon chronic treatment.[148, 150] Recently, combination of GSK1299263 and metformin caused a synergistic weight loss in diet-induced obese mice suggesting potential benefit for obese diabetic patients.[159] Taken together, the above findings suggest that GPR119 agonists have the potential to inhibit feed intake, gastric emptying and body weight gain in rodent studies.

1.4.5 GPR-119 Ligands:

GPR119 is mainly a stimulatory G protein α-subunit (Gas)-coupled G protein-coupled receptor,[139] but it seems to be related to Gai and Gaq and can interact with *β*-arrestin.[160] Identifying its ligands and clarifying related physiological responses are essential to treat diseases.[161] We surveyed and appropriately updated the list of ligands.[162, 163] The ligands are mainly categorized into endogenous ligands (**Table 4**) and synthetic agonists (**Figure 9**). Many studies of GPR119 agonists have focused on their aspects of promoting insulin secretion and improving glucose tolerance. However, Metabolic (dysfunction)-associated fatty liver disease (MAFLD) is correlated with the pathological factors of T2DM, and hence GPR119 agonists have potential as therapeutic agents for alleviating MAFLD.

1.4.5.1 Endogenous ligands of GPR119

Oleoylethanolamide (OEA), Lysophosphatidylcholine (LPC), retinoic acid, palmitoylethanolamide (PEA), arachidonoylethanolamide (AEA) etc., are considered endogenous ligands that activate GPR119 on intestinal endocrine cells (ECCs) to activate adenylate cyclase (AC), thereby increasing the downstream cAMP and increasing the release of incretins, causing a series of physiological effects.[164-167] The rank order of the effectiveness of various ligands to activate GPR119 is first OEA, then

LPC, PEA, stearoyl-ethanol amide (SEA), and finally AEA.[166] The ω-3 unsaturated fatty acid metabolite 5-hydroxy-eicosapentaenoic acid (5-HEPE) also activates GPR119 with an efficacy approximately equal to that of OEA.[168] N-oleoyldopamine (OLDA), a lipid amide, extracted from the bovine striatum is a potent endogenous ligand for GPR119 along with other hydroxybenzyl lipid amides. The potency of OLDA is equivalent to the potency of OEA.[136, 169] In addition, some lysophospholipids and other lipid breakdown products, such as LPC, oleic acid, and 1-Oleoyl glycerol (1-OG), can activate GPR119, but because of their low potency, their activity has not been determined.[170]

LPC: For all the studied lysophospholipids, LPC produced by phospholipase A2 (PLA2) seems to be the most effective in activating GPR119.[170] LPC activates GPR119 to cause glucose-dependent insulin release (GSIS). It has been a promising candidate for anti-T2DM.[171] The earliest discovery, showing that LPC can promote insulin release, was made by Metz et al.[172] who discovered various LPCs in 1986, including LPC 16:0, LPC 18:0, and LPC 18:1, all of which are present in human plasma.[171] Moreover, LPC, as a marker for a variety of liver diseases, is elevated in MAFLD, but saturated LPC is reduced in patients with advanced cirrhosis, and it is associated with mortality risk.[173] In addition, LPC can protect against hepatitis by binding to type II natural killer T cells, produce anti-inflammatory effects in inflammatory diseases, increase anti-inflammatory factor levels and reduce the production of inflammatory mediators, including interleukin-6 (IL-6) and nitric oxide (NO).[174] In contrast, the chemotactic effect of LPC on monocyte chemotactic protein-1 (MCP-1), interleukin-8 (IL-8) and RANTES may have a pro-inflammatory effect.[175]

2-Oleoyl glycerol (2-OG): Being among the most effective natural agonists of GPR119, OEA and 2-monoacylglycerols (2-MAGs), triglyceride metabolites, have been extensively studied, especially 2-OG. Further proved that in triglyceride metabolism, 2-OG activates GPR119 to promote the secretion of incretins, and when combined with GRP40 agonist, has a synergistic effect.[139] Whether 2-OG specifically activates GPR119 is not clear because of the instability of 2-OG itself. First 2-oleyl glyceryl (a 2-OG analogue) was used in GPR119-knockout mice, found that GPR119 improves glucose tolerance and is eliminated by GPR119 antagonists.[176] Human GPR119-transfected COS-7 cells were used and it was confirmed that 2-OG and other

monoacylglycerols activated GPR119 increased the secretion of GLP-1 and other hormones and it was suggested that GPR119 acts as a fat sensor.[137] Interestingly, 2-OG formed by lipoprotein esterase (LDL) acts as a lipid signal transducer in the vascular system.[177]

Oleoylethanolamide (OEA): Oleoylethanolamide, an endogenous fatty acid derivative, is a natural agonist of GPR119.[162, 178] OEA is also a peroxisome proliferator activated receptor α (PPAR-α) agonist that reduces food intake and promotes lipid oxidation.[179] In addition, OEA may reduce fat gain in high-fat diet mice by activating the GPR119 pathway.[177] Studies have shown that bile acids regulate OEA production and activate GPR119 to regulate gastric emptying and increase satiety in experimental mouse models.[180] Hilary A. Overton et al. found that GPR119 at least partially mediated the effect of OEA on food intake, and they orally administered PSN632408, a new GPR19 agonist to rats, which inhibited food intake and white fat accumulation.[132] Similarly, AR6231453, a GPR119 agonist, and found that it inhibited gastric emptying through a GPR119- dependent pathway and prolonged gastric emptying time.[158] However, it is still unclear whether the gastric inhibitory effects of OEA-activated GRP119 are specific. A study in GPR119-knockout mice indicated that GPR119 is unnecessary for the gastric inhibitory effects of OEA.[126] The gastric inhibitory effects produced by OEA may involve pancreatic polypeptide (PPY).[167] OEA can trigger effects similar to those observed after bariatric surgery, including reduced food intake, reduced fat mass, increased GLP-1 release, and reduced lipid levels, which are undoubtedly beneficial to patients with MAFLD.[181] The endogenous ligands and their EC_{50} values are summarized in **Table 4** as a ready reference.

Table 4: Endogenous ligands for GPR-119 agonist.[135]

Name	EC_{50} (μM)
2-Oleoyl glycerol (2-OG)	2.5-17
Oleoylethanolamide (OEA)	0.2-5
N-Oleoyl-dopamine (OLDA)	3.2
Lysophosphatidylethanolamine	5.7
Lysophosphatidylinositol	5.7
Lysophosphatidylserine	>30

Name	EC_{50} (μM)
Lysophosphatidic acid	>30
Sphingosylphosphorylcholine	>30
Oleic acid	>1000
Palmitoyl-lysophosphatidylcholine (16:0-lysoPC)	1.6-2.1
Stearoyl-lysophosphatidylcholine (18:0-lysoPC)	3.3
Oleoyl-lysophosphatidylcholine (18:1-lysoPC)	1.5-9
5-Hydroxy-eicosapentaenoic acid (5-HEPE)	0.03-3
Palmitoylethanolamide (PEA)	0.84
Linoleoylethanolamide (LEA)	0.56-5
2-Linoleoyl glycerol	12
2-Palmitoyl glycerol	11
2-Arachidonoyl glycerol	NA
1-Oleoyl glycerol(1-OG)	2.8
1-Linoleoyl glycerol	36
Anandamide	NA
Oleamide	4.5
N-Arachidonoyldopamine	NA
N-Oleoyl-tyrosine	0.7
Arachidonoyl ethanolamide (AEA)	NA

NA denotes Not Applicable

1.4.5.2 Synthetic GPR119 ligands:

Since GPR 119 is found to be a promising target for the treatment of T2DM, many synthetic ligands were designed/discovered and some of them were disclosed (see Figure 9). Several GPR119 agonists have entered into phase I and II clinical trials. However, not a single molecule has been tested in phase III clinical trials. AR231453 is the first GPR119 agonist developed by Arena Pharmaceuticals (EC_{50} = 0.0047–0.009 μM).[182, 183] AR231453 strongly stimulated glucose-dependent insulin release and cAMP accumulation in cells transfected with human GPR119 and rat islets, but there was almost no response in GPR119- deficient mice or those lacking GPR119 cells.[126] In addition, the use of AR231453 significantly increased the release of GLP-1 from rat intestinal L cells.[183] AR231453 has been used in several pre-clinical studies on

diabetes, showing that it can regulate glucose homeostasis and increase the secretion of incretins.[149, 184]

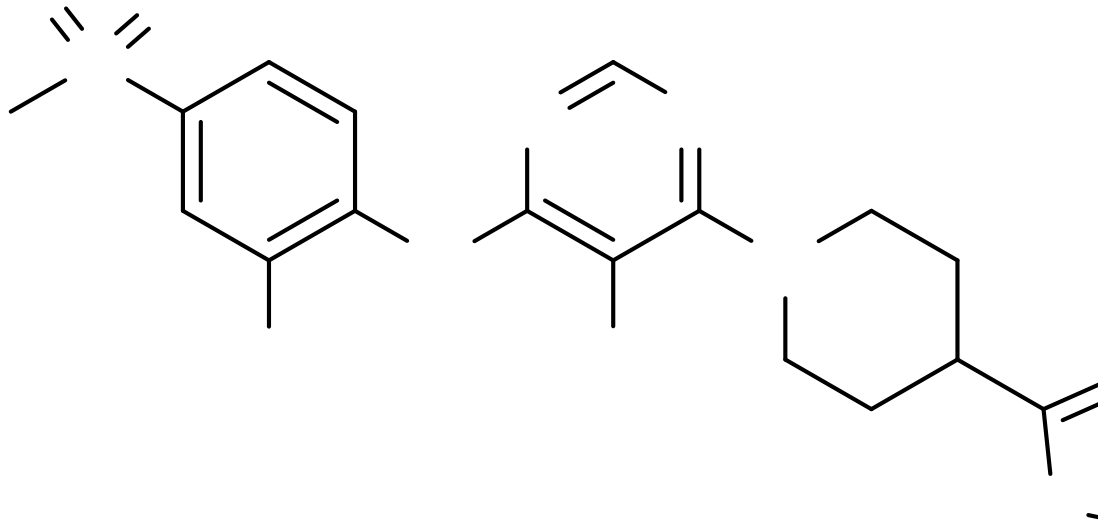

Figure 9: Synthetic ligands for GPR-119 agonist

APD597 (JNJ-38431055) is an orally bioavailable, selective GPR119 agonist that was co-developed by Arena pharmaceuticals and Johnson & Johnson. Some clinical trials have been completed to evaluate its pharmacokinetics, safety, tolerability, and role in obesity and T2DM. JNJ-38431055 (3–30 mg/ kg PO) significantly improved the glucose excursion of diabetic experimental rats.[142] Studies have demonstrated that oral administration of APD597 is safe and well tolerated, and it can increase the secretion of incretin and insulin and decrease incremental plasma glucose excursion during oral glucose tolerance test in T2DM patients, but the final hypoglycemic effect is not ideal.[185] In a double blind, randomized and placebo-controlled study, oral JNJ-38431055 (2.5-800 mg) in healthy male volunteers was found to be safe and well tolerated, and it can increase the concentrations of GLP-1, GIP, and PYY. Compared with the placebo

group, APD597 did not significantly increase insulin secretion or glucose excursion, but it had a higher insulin secretion rate in a graded glucose infusion study.[186]

AS1669058 (EC_{50} = 0.11 μM) is a new generation of GPR119 small molecule agonist reported by Astellas company and further improved from AS1269574 (EC_{50} = 2.5 μM).[187] AS1669058 dose-dependently stimulates insulin secretion in HIT-H15 cells and isolated rat pancreatic islets. Administration of 1 mg/kg of AS1669058 significantly improved the glucose tolerance of ICR mice, and administration of 3 mg/kg of AS1669058 twice a day for a week reduced the glucose level of db/db mice.[145] GSK1292263, a GPR119 agonist from GlaxoSmithKline in its phase II trial did not show significant effect on GLP-1, GIP, Glucagon, glucose, insulin levels and also failed to improve glucose control in type 2 diabetic patients when dosed alone or with Metformin or Sitagliptin. However, it caused significant increase in circulating total PYY levels.[188]

PSN821 from Prosidion Limited (Phase II) was discontinued due to unknown reasons.[174] Another GPR119 agonist, MBX2982 (CymaBay Therapeutics) successfully reduced postprandial glucose levels in type 2 diabetic patients and increased insulin and incretin levels in a 4 weeks long phase II clinical trial; however, it was also discontinued.[189, 190]

Recently, LEZ763, a novel GPR119 agonist demonstrated significant increase in GLP-1, GIP, and PYY levels but was unable to lower postprandial glucose levels significantly in diabetic patients. The increase in glucagon levels caused by LEZ763 was assumed to be the cause of undesirable clinical consequence in phase II trial.[191] BMS-903452, a novel GPR119 agonist has completed its phase I trial; however, no further development has been reported since April 2016.[192]

The reasons for lack of clinical efficacy for GPR119 agonists still remain unknown, however for some of them like AR-7946 (preclinical) or GSK1192263, it was reported that they showed loss of efficacy in clinical trials either due to tachyphylaxis or agonist induced desensitization of GPR119 receptors.[174] However, this is not the case for all other GPR119 agonists. For example, MBX2982 (phase II) showed reduction in glucose levels in diabetic patients. Thus, tachyphylaxis appears to be a compound related (GSK1292263) rather than GPR119 target specific concern. Therefore, the lack of

glycemic efficacy may be due to species differences in pharmacodynamics or pharmacokinetic and limitations in physicochemical properties of the currently available compounds.[146] On the other hand, few GPR119 agonists such as APD668, YH18421 and DA-1241 did not show loss of efficacy even after repeated administration (once daily regimen) in rodent studies.[126, 171, 178] Interestingly, repeat administration of GSK1292263 significantly improved lipid profile in diabetic and non-diabetic dyslipidaemic subjects.[193, 194] Recently, DS-8005a (Phase II) demonstrated significant reductions in triglyceride, total cholesterol, LDL cholesterol and a trend towards increase in HDL cholesterol levels in Japanese type 2 diabetes patients.[195] Therefore, the current focus has shifted to profiling of GPR119 agonists as anti-dyslipidaemia agents even if they could have failed as anti-diabetic drugs.[174]

1.4.6 Future prospects and challenges

Metabolex and Sanofi-Aventis signed a massive agreement to develop the latest GPR119 pharmacological agent.[196] Although there are currently approved injections of liraglutide and exenatide that directly target GLP-1, the discovery of GPCRs has led to opportunities for innovative development of oral active drugs[196], and there are many GPR119 agonists which are under clinical trials (**Table 5**).

Table 5: Some GPR-119 agonists under clinical trials [135]

Name	Condition or Disease & clinical trials. gov number	Sponsor
Oleoyl glycerol	Type 2 diabetes (NCT01043445)	Glostrup University Hospital, Copenhagen.
	Type 2 diabetes (NCT02264951)	Glostrup University Hospital, Copenhagen.
MBX-2982	Type 2 diabetes (NCT01035879)	CymaBay Therapeutics, Inc
	Type 1 diabetes (NCT04432090)	Translational Research Institute for Metabolism and Diabetes, Florida
GSK1292263	Healthy Volunteers (NCT00783549)	GlaxoSmithKline
	Type 2 diabetes (NCT01128621)	GlaxoSmithKline
	Type 2 diabetes (NCT01119846)	GlaxoSmithKline
	Dyslipidemia (NCT01218204)	GlaxoSmithKline
PSN821	Type 2 diabetes (NCT01386099)	Prosidion Ltd
JNJ-38431055	Healthy Male Volunteers (NCT00910923)	Johnson & Johnson Pharmaceutical Research & Development, L.L.C

	Healthy overweight or obese adult male Volunteers (NCT01054118)	Johnson & Johnson Pharmaceutical Research & Development, L.L.C
	Type 2 diabetes (NCT00946972)	Johnson & Johnson Pharmaceutical Research & Development, L.L.C
DS-8500a	Healthy Subjects (NCT03699774)	Daiichi Sankyo, Inc
	Type 2 diabetes (NCT02685345)	Daiichi Sankyo, Inc
	Type 2 diabetes (NCT02669732)	Daiichi Sankyo, Inc
	Type 2 diabetes (NCT02222350)	Daiichi Sankyo, Inc
	Type 2 diabetes (NCT02628392)	Daiichi Sankyo, Inc
	Type 2 diabetes (NCT02647320)	Daiichi Sankyo, Inc
LEZ763	Normal Healthy Volunteers and patients with type 2 diabetes (NCT01619332)	Novartis Pharmaceuticals
BMS-903452	Normal Healthy Volunteers and patients with type 2 diabetes (NCT01240980)	Bristol-Myers Squibb
APD668	Discontinued	Arena
“NN”	Discontinued	Novartis
DA-1241	Type 2 diabetes (NCT03061981)	Dong-A ST Co., Ltd
	Type 2 diabetes (NCT03646721)	Dong-A ST Co., Ltd

GPR119 is highly expressed in the digestive system, such as the gastrointestinal pancreas, and there is a little evidence that it is expressed in the human central nervous system; thus, adverse side effects in the nervous system are avoided. Another problem for GPR119 treatment is the development of related candidate compounds. Although there are currently excellent specific GPR119 agonists, their efficacy is a competing element affecting the future drug development market, and there are excellent comments and discussions on this aspect of drug development.[187] Although most of the current clinical trials of GPR119 have focused on treating T2DM, and some of the experimental results are not ideal, the safety and tolerability of MBX-2982 and PSN821 are worthy of recognition, and GLP-1 secretion is increased. Therefore, as long as chronic metabolic diseases such as MAFLD continue to exist and no specific drug is found, comprehensive investigation into potential effects of GPR119 and well-designed clinical trials still need to be conducted. In addition, the GPR119 sequence of rodents and humans are different, so there may be differences in the translation of results based on various rodent experimental models to clinical practice, which is also an important factor that should be considered.[197]

These facts made the development of GPR-119 agonists with distinct biological and safety profiles a challenge among the drug discovery groups around the world, as the medical need for diabetes mellitus has largely remained unmet.