DIABETES MELLITUS TYPE 2 : NEW PHARMACOLOGIC AGENTS

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Diabetes Mellitus Type 2 : New Pharmacologic Agents

ANCC Accredited NCPD Hours: 3 hrs

Target Audience: RN/APRN

Need Assessment

It is predicted that, in 2040, there will be more than 640 million people with diabetes worldwide. Therapeutic options for diabetes management have expanded dramatically in the last five years. Advanced practice nurses are ideally suited to play an integral role in the education and medical management of people with diabetes. The combination of clinical skills and expertise in teaching and counselling enhances the delivery of care in a manner that is both cost-reducing and effective. Inherent in the role of practice nurses is the understanding of shared responsibility for health care outcomes. This partnering of nurse with patient not only improves care but strengthens the patient's role as self-manager.

Objectives

- Discuss the pathogenesis of Type 2 diabetes mellitus
- Describe the clinical diagnosis of Type 2 diabetes mellitus
- Identify four pharmacologic agents in the management of Type 2 diabetes mellitus
- Recognise the combination of antidiabetic agents in management of Type 2 diabetes mellitus.
- Describe the future perspectives and novel researches in Diabetes mellitus.

Goal

The goal of this article is to review current and future treatments for patients with T2DM, its use in clinical practice and in special situations, with an emphasis on agents introduced within the last decade

Introduction

Type 2 diabetes mellitus (T2DM) is a disease that affects more than 400 million people around the world. The prevalence of T2DM is expected to double within the next 20 years, due to the increase of the age, obesity and the number of ethnic groups of high risk in the population, with significant increases in cardiovascular disease, end-stage renal disease (ESRD), retinopathy and neuropathy. Additionally, to achieve good metabolic control in diabetes and keep long term, a combination of changes in lifestyle and pharmacological treatment is necessary. Achieving near-normal glycated hemoglobin (HbA1c) significantly decreases risk of macrovascular and microvascular complications. However, only about 50% of diabetic patients reach their HbA1c target. Algorithms for the treatment of diabetes highlight the need for good glycaemic control to reduce the development or progression of diabetes complications. In recent years increased the number hypoglycaemic agents available for the treatment of T2DM has increased. A recent position statement of the American Diabetes Association (ADA) and the European Association for the Study of Diabetes (EASD) on a patient-centered approach in the management of patients with T2DM gives an overview on how different conditions and co-morbidities may influence the choice of different hypoglycaemic agents. The ADA/EASD suggests that initial intervention should focus on lifestyle changes. Moreover, changes in lifestyle have proven to be beneficial, but for many patients is a complication keep long term, due to differing experiences or perceptions. In general, drug therapy includes not only initial hypoglycaemic agents, but other intensification strategies to maintain glycaemic control over time, often requiring several drugs with different mechanisms of action. Physicians should be familiar with the different types of existing drugs for the treatment of diabetes and select the most effective, safe and better tolerated by patients. [1, Rank 4]

Pathogenesis of Type 2 Diabetes Mellitus

Diabetes mellitus belongs to the most rapidly increasing diseases worldwide. Among the consequences of diabetes are micro- and macrovascular complications such as retinopathy and nephropathy leading to blindness and renal insufficiency, respectively, and cardiovascular and cerebrovascular diseases. Indeed, more than 60% of type 2 diabetics die of myocardial infarction or stroke. In general, two forms of diabetes mellitus are distinguished: type 1 diabetes is caused by the autoimmune destruction of the insulin-producing

beta-cells in early childhood and resulting in an absolute lack of insulin. For the development of type 2 diabetes, obesity caused by the chronic imbalance between calorie intake and energy expenditure is the major risk factor. The excess of nutrients is stored mainly in the white adipose tissue (WAT), the liver and the skeletal muscle. However, under conditions of chronic over-nutrition, their storage capacity is eventually exceeded and mitochondrial dysfunction, oxidative stress, endothelial reticulum stress and abnormal post-translational modification of intracellular proteins ensue.

The cellular stress activates diverse signalling pathways, including the JNKs and the IκB kinase β (IKKβ), which, in turn, inhibit insulin signalling pathways and trigger inflammation within the WAT (White adipose tissue) and other tissues. This subacute inflammation within the metabolic tissues leads to increased secretion of pro-inflammatory cytokines, which reinforces inflammatory signals and decreases the secretion of protective factors such as adiponectin. Furthermore, mainly via inhibitory serine/threonine phosphorylation of the insulin receptor substrate 1, some pro-inflammatory cytokines inhibit insulin signalling, thereby escalating insulin resistance. In this scenario, insulin resistance might be considered protective as it prevents the further excess uptake of nutrients and the deterioration of the cells within the metabolic tissues. Deregulated nutrient uptake itself can activate inflammation by

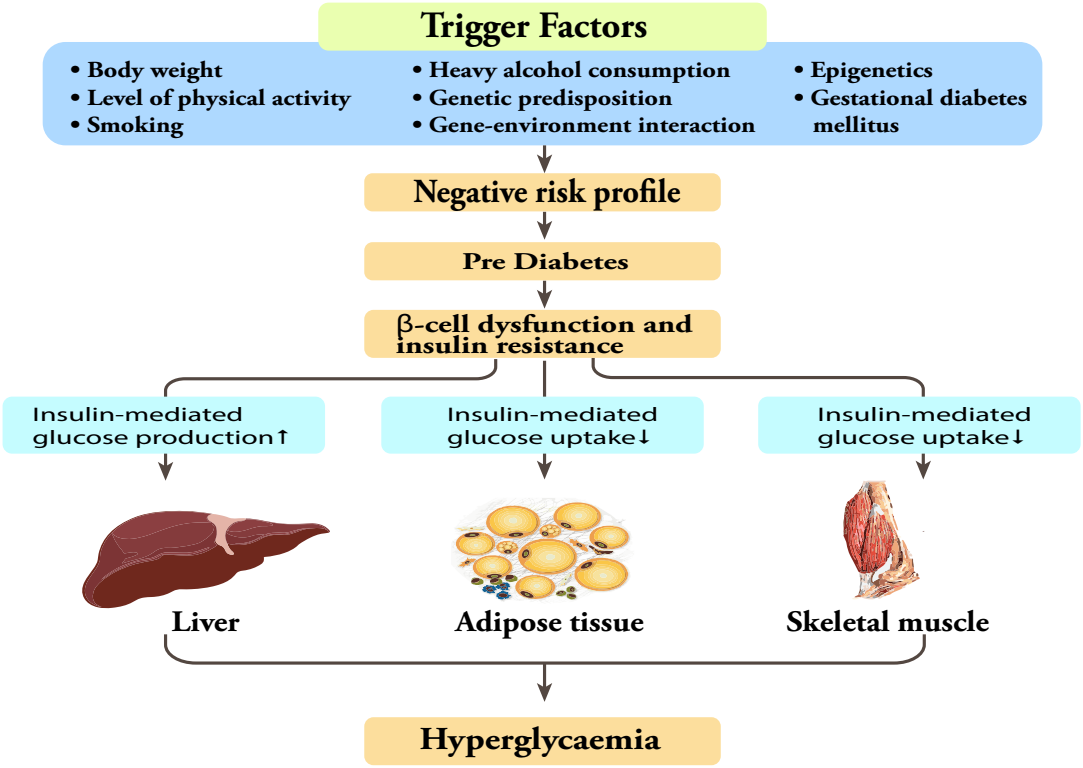

Figure 1: Pathophysiology of Type 2 Diabetes Mellitus

various mechanisms. Thus, obesity-induced insulin resistance contributing to the low-grade inflammation of metabolic tissues and the low-grade inflammation contributing to insulin resistance perpetuate each other.

An ominous octet that leads to hyperglycemia, which occurs in isolation or in combination, has been proposed for eight pathophysiological mechanisms underlying T2DM (as shown in Figure 2)

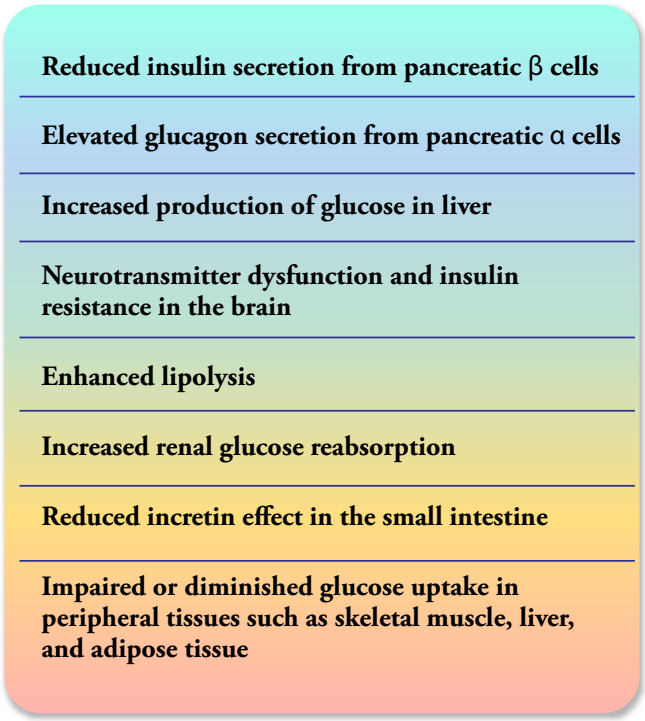

Figure 2: Ominous octet of hyperglycemia,

Currently available glucose-lowering therapies target one or more of these key pathways.

Dysfunction of the beta-cells with regard to insulin secretion and biosynthesis and a reduction of beta-cell mass were demonstrated in patients suffering from type 2 diabetes or impaired glucose tolerance. Hence, the targets of an optimal anti-diabetic therapy are the attenuation of the inflammation of metabolic tissues and insulin resistance and the restoration or at least the amelioration of beta-cell function and mass to ultimately prevent the development of micro- and macrovascular complications. [2, Rank 3]

> **" To compensate for the increased insulin demand under conditions of insulin resistance, beta-cell hypertrophy and hyperplasia develops, leading to hyperinsulinaemia. It should be noted that most of the obese, insulin-resistant humans do not become diabetic, implying additional mechanisms for the pathogenesis of type 2 diabetes mellitus. "**

Pathogenesis of Diabetes in the Elderly

Aging is a process characterized by a multifaceted interaction of genetic, epigenetic, and environmental factors. Genetic variants have been shown to impact on human longevity, showing a strict association with both unsuccessful aging and diabetes. A strong genetic predisposition to Type 2 Diabetes Mellitus in the elderly is apparent as well though only some candi-

date genes have been identified. The pathogenesis of Type 2 Diabetes Mellitus is characterized by two major mechanisms: impaired β-cell function and insulin resistance. The former is the main defect observed in lean older subjects, while obese older patients have relatively normal insulin secretion but marked resistance to insulin-mediated glucose disposal. The Cardiovascular Health Study showed that the association between some risk factors and incident Diabetes Mellitus varied significantly depending on whether Diabetes Mellitus was preceded predominantly by insulin resistance, β-cell dysfunction, or both, thus suggesting putative subtypes of Diabetes Mellitus with biologic and clinical implications. With aging, glucose-stimulated insulin response tends to decline, impaired insulin secretion pulsatility is lost, decreased sensitivity to incretins develops, andβ-cell mass is reduced. Many events contribute to the age-related loss of β-cell mass and function, including the age-associated mitochondrial dysfunction, as well as increased oxidative stress and inflammation.

Aging results in a progressive loss of muscle mass and strength called "sarcopenia" that has a complex etiology involving neuronal, hormonal, immunological, nutritional and physical activity mechanisms. Muscle mass loss in the elderly is associated with an increased fat mass infiltration that has been shown to be associated with worsened insulin sensitivity.

In this regard, in a recent cross-sectional study of 301 non diabetic subjects with a mean age of 65.9 years, a strong association between insulin resistance and relative muscle mass has been described. Similarly, an association between sarcopenia and insulin resistance, diabetes, and metabolic syndrome has been reported in a large Korean population, particularly in elderly participants. The link between sarcopenia and insulin resistance is a complex one, most likely mediated by several factors (i.e. mitochondrial dysfunction, reactive oxygen species, subtypes of adipocytes, fat-associated inflammation and adipocytokines). Anyway, though sarcopenia may be not the primary cause of skeletal muscle insulin resistance in the elderly subjects, loss of lean muscle mass can be considered a worsening determinant. [12, Rank 5]

Moreover, poor dietary habits and decreased physical activity all contribute to reduce insulin sensitivity in older population. Glucose metabolism in older people can also be affected by co-existing illnesses and polypharmacy. Finally, autoimmune phenomena may play a role in the pathogenesis of type 2 diabetes in a subset of older patients.

Although understanding of the pathogenesis of type 2 diabetes has

advanced rapidly, the underlying molecular mechanisms remain partially unknown even because they are multiple, complex and linked each other. There is a huge progress in aging research on the role of the nutrient sensor mammalian target of rapamycin (mTOR) in aging and age-related diseases, including insulin resistance. mTOR integrates multiple signals including growth factors, hormones, and cellular energy levels to regulate protein translation and cell metabloism, and survival, thus mediating the nutrient effects on insulin resistance. The attractive link between mammalian target of rapamycin and insulin signaling cascades suggests that mammalian target of rapamycin could become a therapeutic target in insulin-resistant status, even if its clinical application in metablic diseases is still limited. In summary, diabetes in the elderly is the result of a tangled and still incompletely understood combination of genetic and environmental factors that overlap and are magnified by the ageing process. [11, Rank 3]

Clinical Diagnosis of Type 2 Diabetes

Diabetes may be identified in low-risk individuals who have spontaneous glucose testing during routine primary clinical care, in individuals examined for diabetes risk assessment, and in frankly symptomatic patients. Early diagnosis of T2DM can be accomplished through blood tests that measure PG levels. FPG is the most common test to detect diabetes: a level of ≥ 126 mg/dL or 7.0 mmol/ L confirmed by repeating the test on another clinic visit effectively diagnoses the disease. This test requires fasting for at least the previous 8 h and generates enhanced reliability when blood is drawn in the morning. Another criterion is the 2 h PG of ≥200 mg/dL or 11.1 mmol/ L in a patient presenting with the traditional symptoms of diabetes such as polyuria, polydipsia, and/or unexplained weight loss. A positive 2-h OGTT will show a PG level of ≥200 mg/dL or 11.1 mmol/ L after a glucose load containing 75 g of glucose solution in water. Two-hour PG OGTT is not commonly used in the clinic because, although it is more sensitive than FPG test, it is less convenient and more expensive for patients. Additionally, this test holds less relevance in routine follow-ups after confirmed diagnosis of diabetes is obtained.

In the past, the glycated hemoglobin (HbA1C) test was used mainly to monitor the adequacy of glycemic management and has strong predictive value for diabetes complications. HbA1C is a chronic marker of hyperglycemia and reflects patient's blood glucose level over a period of 3–4 months, coinciding with the lifespan of the

red blood cells (RBCs). HbA1C level is reported in percentages, and a normal level is below 5.7%. The main advantage of the HbA1C test over other blood glucose tests is the convenience it offers to patients; it does not require fasting and can be done at any time of the day. However, this test is more expensive and may not be readily available in certain locations, which may limit its usefulness. There are limited data supporting the use of A1C in diagnosing T2DM in children and adolescents. Although A1C is not routinely suggested for diagnosis of diabetes in children with cystic fibrosis or symptoms that portend development of acute onset of T1DM, the ADA recommends HbA1C for diagnosis of T2DM in children and adolescents.

" HbA1C may be inaccurate in conditions such as anemia, hemolysis, and other hemoglobinopathies like sickle cell disease and hemoglobin (Hb) variants like HbC, HbE, and HbD, as well as elevated fetal hemoglobin. In conditions associated with increased RBC breakdown, such as in the advanced trimesters of pregnancy, recent hemorrhage, intravascular hemolysis or transfusion or erythropoietin treatment, only blood glucose estimation should be used to diagnose diabetes. "

In order to accurately diagnose diabetes and in the absence of frank hyperglycemia (PG>200mg/ dL) or hyperglycemic crisis, it is useful to repeat the same diagnostic test for confirmation. In situations where there are two different tests with conflicting results, the test which is positive should be repeated and a diagnosis of diabetes is made after a confirmatory test has been done. For individuals whose test result/s returned negative for diabetes, repeat testing at 3-year intervals is suggested.

The ADA and American Association of Clinical Endocrinologists recommend screening for prediabetes beginning at age 45 years or earlier for asymptomatic individuals with strong risk factors such as obesity (BMI ≥ 25 kg/m2), hypertension and family history (first degree relative with diabetes). IFG level of 100–125mg/dL (5.6–6.9 mmol/L), IGT with a 2-h OGTT PG level between 140 and 199mg/dL (7.9–11.0 mmol/L), or an HbA1C of 5.7–6.4% indicates prediabetes. Patients with an HbA1C level of >6% are considered high risk of developing diabetes, and early detection is necessary to prevent adverse outcomes. Patients diagnosed with prediabetes can be retested after a year; however, without proper intervention 70% of individuals diagnosed with prediabetes are most likely to progress to diabetes in 10

years or even less, depending on their risk factors. It is also important to note that pre-diabetes may be associated with obesity, dyslipidemia, and hypertension; therefore, lifestyle changes such as healthy diet, physical activity, and cessation of smoking, in addition to the introduction of pharmacological agents, are deemed important to stop or delay the timeline of development of diabetes. [3, Rank 4]

Special thoughts for elderly patients affected by type 2 diabetes mellitus

T2DM can be independently associated with various aging phenotypes collectively defined as geriatric syndromes. These geriatric conditions should be referred to as a third category of diabetic complications and include cognitive impairment and dementia, depression, reduced muscle strength and quality, disability, falls and fall-related morbidity, as well as urinary incontinence.

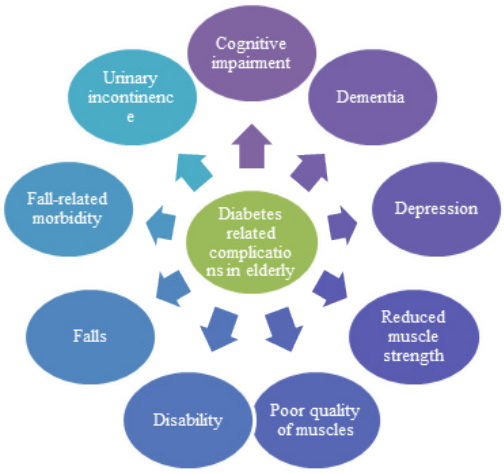

Figure 3: DM related complications in Elderly

These clinical conditions are very frequent in older diabetic people, especially in the frail ones. When present they exert a negative effect on the quality of life, functional outcomes, and mortality. Moreover, these impairments, in particular cognitive decline, can affect in a significant manner the self-management of diabetes. The cognitive decline is likely to initiate early in the natural progression of diabetes and it correlates with overall glycemic control. To emphasize the link between T2DM and cognitive function some authors have proposed Alzheimer's disease as a third form of diabetes. The etiology of cognitive impairment in diabetic patients is multifactorial with a role played by dysglycemia, microvascular disease, and insulin resistance, hyper-phosphorylation of tau protein, amyloid-β deposition, inflammation and oxidative stress. More recently a role for sirtuins has been claimed. Sirtuins belong to a family of highly conserved protein deacetylases that depend on nicotinamide adenine dinucleotide (NAD+) for their activity. These proteins have been shown to influence the course of several neurodegenerative disorders by controlling transcription factor activity. Expression of SIRT1, the best characterized member within the family of sirtuins, seems to be reduced in T2DM and in conditions of insulin resistance, while, its activation improves insulin sensitivity.

Older diabetic people may be more vulnerable also because of coexisting comorbidities and related polypharmacy. Moreover, aging may be associated with changes in several pharmacokinetic and pharmaco-dynamic parameters. These include reduction of renal and hepatic function and increased volume of distribution of lipid soluble drugs resulting in an increase of drug half-life. Pharmacodynamic changes can cause drug accumulation in the circulation and intensified sensitivity, for instance, to sulfonylureas thus increasing the risk of hypoglycemia. In this setting, aging per se is a strong predictor of hypoglycemia and hypoglycemia, in turn, is a major complicating factor of antidiabetic treatment. Impaired counterregulatory response and increased symptom threshold worsen the risk and outcomes of hypoglycemia in elderly diabetic patients. The risk of such an event in the elderly can be by reduced or irregular eating pattern, intercurrent diseases and concomitant use of other drugs Altogether, the various degree of concomitance of these factors may account for the variable rate of hypoglycaemia in the elderly reported in the literature. In the ACCORD trial, each one year increment in baseline age was associated with a 3% increase in the risk for hypoglycaemia requiring medical assistance.

" Patients on five or more medications, particularly if they include ACE-inhibitors and nonselective beta-adrenoceptor antagonists, are more prone to drug-induced hypoglycemia. "

Hypoglycaemia in the elderly is associated with serious morbidity, including cardiovascular events, stroke, arrhythmias, and falls result in fractures on a background of osteoporosis. Results of post-hoc analyses of both the ACCORD and VADT trials have shown a strong association between severe hypoglycemia and cardiovascular mortality, especially in the elderly population. In the ACCORD trial, intensive glucose lowering increased the risk of cardiovascular disease and total mortality in younger participants whereas it had a neutral effect in older participants, though the older subgroup had a greater annualized rate of severe hypoglycemic episodes. Prevention of hypoglycemia requires identification of risk factors, patient and family education and reassurance regarding prevention, detection, and treatment of hypoglycemic events.

However, the heterogeneity of the older diabetic population must be fully appreciated if adequate glycemic control has to be provided. Optimal care should balance health and function, tapering and

tailoring the pharmacological approach in order to reach invidualized goals while avoiding clinical inertia. Biological rather than chronological age of the patient should be considered in defining therapeutic strategies. Assessment of psychological age and social age is also recommended as part of a comprehensive (and multidisciplinary) geriatric appraisal of older people with diabetes in order to address the role of various comorbidities and polypharmacy before selecting treatment plans. [10, Rank 4]

Pharmacologic Management of Type 2 Diabetes Mellitus

Good glycaemic control remains the main foundation of managing Type 2 Diabetes Mellitus. Such approaches play a vital role in preventing or delaying the onset and progression of diabetic complications. It is important that a patient-centered approach should be used to guide the choice of pharmacological agents. The factors to be considered include efficacy, cost, potential side effects, weight gain, comorbidities, hypoglycemia risk, and patient preferences. Pharmacological treatment of type 2 diabetes mellitus should be initiated when glycemic control is not achieved or if HbA1C rises to 6.5% after 2–3 months of lifestyle intervention. Not delaying treatment and motivating patients to initiate pharmacotherapy can considerably prevent the risk of the irreversible microvascular complications such as retinopathy and glomerular damage. Monotherapy with an oral medication should be started concomitantly with intensive lifestyle management.

The major classes of antidiabetic treatment options include 6 categories. (as shown in Figure 4)

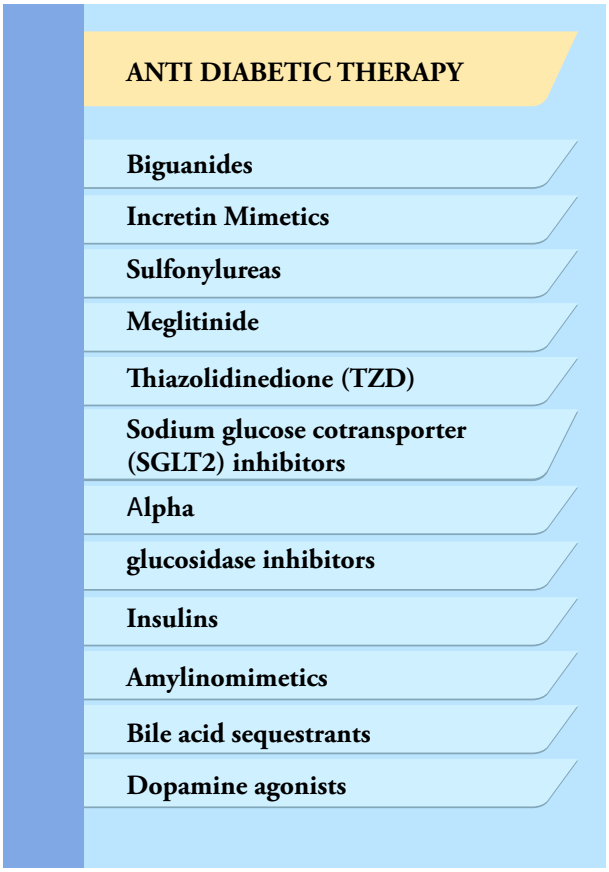

Figure 4: Antidiabetic agents

The current drugs for treating type 2 diabetes mellitus can be roughly distinguished into those acting directly on beta-cells and those that do not. Sulfonylureas such as glibenclamide, tolbutamide and glimepiride have been in use. By inhibition of the ATP-dependent potassium

channel (KATP, KIR6.2) favouring membrane depolarization and subsequent calcium influx through the voltage-dependent L-type calcium channel (Cav1.x), they directly stimulate insulin secretion from the beta-cells. Increased insulin levels reduce blood glucose concentration but lead to weight gain, a most undesired effect in the typical obese type 2 diabetic. Another important adverse effect is hypoglycaemia. The United Kingdom Prospective Diabetes Study (UKPDS) demonstrated a significant reduction of microvascular complications after long-term treatment with glibenclamide (UKPDS 33). In two observational studies, a higher risk for myocardial infarction and for mortality was found in patients treated with glibenclamide in comparison to treatment with glimepiride and gliclazide. Another observational study found a higher incidence of cardiac events under glibenclamide in comparison to gliclazide only in patients with previously known ischaemic heart disease.

In addition to glucose, glucagon-like peptide-1 (GLP-1) secreted from the intestinal L-cells in response to meal ingestion is another important insulin secretagogue. The short plasma half-life of GLP-1 of 2 min due to cleavage by dipeptidylpeptidase 4 makes the substitution of GLP-1 itself unsuitable. Therefore, s.c. injectable GLP-1 analogues with a mutated (i.e. exenatide) or a masked DPP 4 cleavage site (i.e. liraglutide) or orally available DPP 4 inhibitors (the gliptins sitagliptin, vildagliptin, saxagliptin) raising the endogenous GLP-1 levels are used. GLP-1 analogues and the gliptins have attracted much attention in the past years. As GLP-1 potentiates insulin secretion only in the presence of elevated glucose levels, the possibility of hypoglycaemic events is rather low. In rodents and in humans, GLP-1 has been shown to improve beta-cell function and increase beta-cell mass.

In addition, GLP-1 promotes satiety, slows down gastric emptying, inhibits the secretion of the glucogenic hormone glucagon from α-cells and results in weight loss. However, recent reports have raised concerns about the safety profile of the GLP-1 receptor agonists and the DPP 4 inhibitors. In rodents, treatment with the long-acting GLP-1 receptor agonist exendin resulted in acinar cell death and inflammation and in accelerated metaplasia and lesion formation of pancreatic intraepithelial neoplasia. In humans, GLP-1-based therapy leads to increased proliferation and dysplasia within the exocrine pancreas and a meta-analysis revealed an association between GLP-1 therapy and increased risk for hospitalization for acute pancreatitis. In contrast, two recent studies evaluating the cardiovascular safety of saxagliptin and alogliptin, respec-

tively, reported no increase in the incidence of pancreatitis; a slightly increased risk of heart failure was observed in the saxagliptin group. It remains to be seen whether the undoubted benefits of GLP-1-based therapy outweigh its potential risks.

As a result of the The UK Prospective Diabetes Study, the biguanide metformin experienced a revival of its use and is now the first-choice anti-diabetic drug. A rare but potentially lethal effect is lactic acidosis, with an incidence of 4.3 cases in 100 000 patient-years. Still, there are several contraindications for metformin use, including cardiovascular, renal, hepatic and pulmonary diseases. In the case of metformin, the beneficial effects clearly outweigh its potential risks: metformin was shown to prevent cardiovascular mortality and disease (UKPDS 34, 1998) and might reduce cancer incidence. In male mice, long-term treatment with metformin extended their lifespan. In pre-diabetic humans, both lifestyle intervention and metformin reduced the incidence of diabetes, but lifestyle intervention was more effective.

" Metformin lowers blood glucose levels mainly through inhibition of hepatic gluconeogenesis; enhanced glucose uptake into the skeletal muscle has also been described. Metformin is weight neutral. "

Inhibition of complex I in the mitochondrial electron transport chain, resulting in energy depletion with increased ADP/ATP and AMP/ATP (Adenosine monophosphate/ Adenosine tri phosphate) ratios and activation of the Adenosine monophosphate (AMPK), a central cellular energy sensor and regulator of energy homeostasis have been proposed. Consistent with this, infusion of the direct activator of Adenosine monophosphate, 5-aminoimidazole-4-carboxamide riboside (AICAR) decreased hepatic glucose output, thus lowering blood glucose levels in type 2 diabetic patients. Researchers suggested that Adenosine monophosphate induced inhibition of the cAMP-regulated transcriptional co-activator (CRTC) 2 prevents the expression of gluconeogenic genes in hepatocytes, consistent with the findings that cAMP-regulated transcriptional co-activator 2 plays a pivotal role in hepatic glucose output under fasting conditions. However, metformin still exerted hypoglycaemic effects in mice lacking Adenosine monophosphate in the liver, suggesting that AMPK – and transcription-independent mechanisms – confer metformin-caused reduction of hepatic gluconeogenesis. Another Adenosine monophosphate independent mechanism of metformin action was proposed,

showing that metformin attenuated glucagon-induced hepatic gluconeogenesis, by indirectly inhibiting the adenylate cyclase. Metformin is a hydrophilic base and is transported via organic cationic transporters (OCT) 1 and 2 into the liver, the gut and the kidney. In organic cationic transporters 1-deficient mice, hepatic metformin concentration was decreased and the drug no longer reduced fasting blood glucose levels, suggesting that organic cationic transporters 1 is important for hepatic metformin action.

From a pathophysiological point of view, the thiazolidinediones have a very favourable pattern of action: they enhance insulin sensitivity of skeletal muscle and liver, inhibit hepatic gluconeogenesis and are anti-inflammatory in various organs. However, fluid retention with associated peripheral oedema due to altered renal sodium and water reabsorption, the higher rate of fractures due to decreased bone formation and increased bone resorption, and the weight gain, in part, due to increased food intake and to increased adipogenesis greatly diminished the widespread use of rosiglitazone and pioglitazone. Whereas pioglitazone was suggested to exert modest protective effects on the CVS, rosiglitazone has been associated with an increased risk of myocardial infarction, resulting in the withdrawal of this drug. However, rosiglitazone's increased risk of myocardial infarction remains a matter of debate, whereas an increased risk for heart failure is well documented for the thiazolidinediones. In addition, increased incidence of bladder cancer has been reported for pioglitazone. Thiazolidinediones are agonists of the PPARγ (NR1C), a nuclear receptor that forms permissive heterodimers with retinoid X receptors. Specific endogenous PPARγ ligands are still elusive, but some fatty acids and their derivatives can bind and activate this nuclear receptor. In addition to ligand binding, PPARγ activity is regulated by post-translational modifications, among them phosphorylation by distinct kinases, acetylation, sumoylation and ubiquitination, thereby expanding the cell- or tissue-specific modulation of this nuclear receptor.

To prevent the adverse effects of thiazolidinediones, but retaining the desired effects, in analogy to the selective oestrogen receptor modulators, selective PPAR modulators might be promising new anti-diabetic drugs. Dual PPARγ/α agonists represent an approach to combine the glucose-lowering effects of the PPARγ agonists with the lipid-lowering effects of the PPARα agonists (like the fibrates) to effectively manage glycaemic control and improve cardiovascular outcome in type 2 diabetic patients. Several dual agonists, called

glitazars, have been developed with promising effects on lowering HbA1c and plasma lipid levels. However, due to diverse safety concerns, the further development and in the case of aliglitazar phase 3 clinical trials were stopped. Whereas the glucose-lowering effect of thiazolidinediones is due to many actions, dapagliflozin exerts its effect through inhibition of the sodium-glucose transporter 2 (SGLT2) in the proximal tubule of the kidney, thus preventing glucose reabsorption. The SGLT2 is a low-affinity, high-capacity transporter, reabsorbing most of the glucose in the urine. Its inhibition cannot result in hypoglycaemia because a fraction of the remaining glucose is reabsorbed by the SGLT1, a high-affinity, low-capacity transporter that is expressed in the more distal

Biguanide

It is not a novel agent. The discovery of biguanide and its derivatives for the management of diabetes started in the middle ages. Galega officinalis, a herbaceous plant, was found to contain guanidine, galegine, and biguanide, which decreased blood glucose levels. Metformin is a biguanide that is the main first-line oral drug of choice in the management of T2DM across all age groups. Metformin activates adenosine monophosphate-activated protein kinase in the liver, causing hepatic uptake of glucose and inhibiting gluconeogenesis through complex effects on the mitochondrial enzymes. Metformin is highly tolerated and has only mild side effects, low risk of hypoglycemia and low chances of weight gain. Metformin is shown to delay the progression of Type 2 Diabetes Mellitus, reduce the risk of complications, and reduce mortality rates in patients by decreasing hepatic glucose synthesis (gluconeogenesis) and sensitizing peripheral tissues to insulin. Furthermore, it improves insulin sensitivity by activating insulin receptor expression and enhancing tyrosine kinase activity. Recent evidence also suggest that metformin lowers plasma lipid levels through a peroxisome proliferator-activated receptor (PPAR)-α pathway, which prevents cardio vascular diseases. Reduction of food intake possibly occurs by glucagon-like peptide-1 (GLP-1)-mediated incretin-like actions. Metformin may thus induce modest weight loss in overweight and obese individuals at risk for diabetes.

“ Metformin is contraindicated in patients with advanced stages of renal insufficiency, indicated by a glomerular filtration rate (GFR) ‹30mL/min/1.73m2. If metformin is used when GFR is significantly diminished. ”

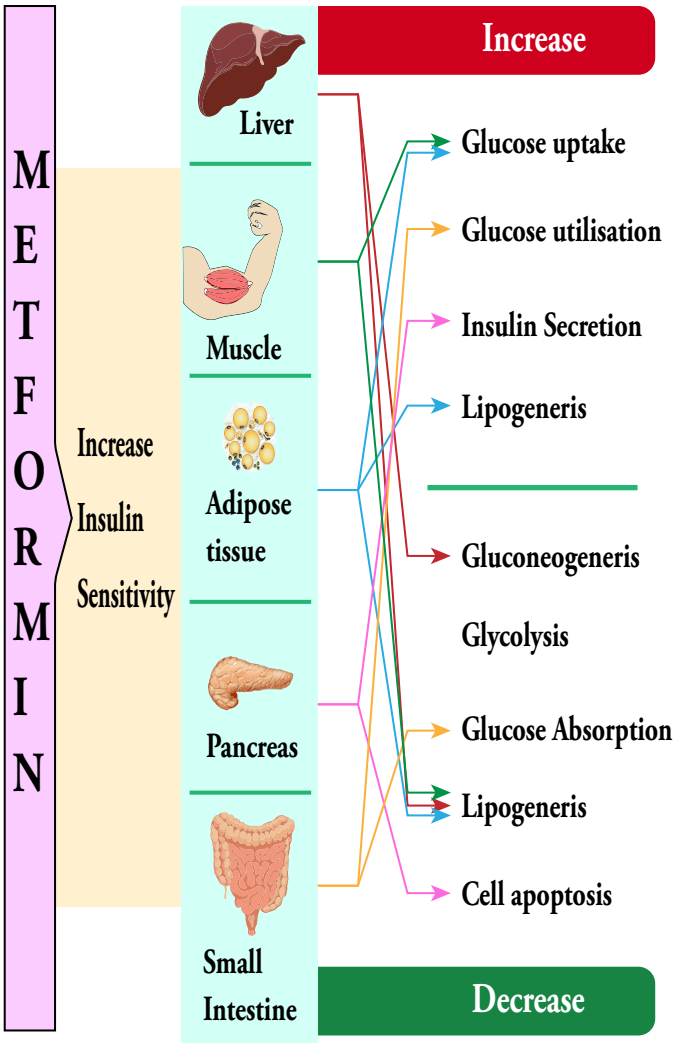

Figure 5: Action of Metformin

Once ingested, metformin (with a half-life of approximately 5 h) is absorbed by organic cation transporters and remains unmetabolized in the body and is widely distributed into different tissues such as intestine, liver, and kidney. The primary route of elimination is via kidney. The dose should be reduced and patients should be advised to discontinue the medication if nausea, vomiting, and dehydration arise from any other cause (to prevent ketoacidosis). It is important to assess renal function prior to starting this medication.

Metformin has an excellent safety profile, though may cause gastrointestinal disturbances including diarrhea, nausea, and dyspepsia in almost 30% of subjects after initiation. Introduction of metformin at low doses often improve tolerance. Extended release preparations seldom cause any gastrointestinal issues. Very rarely, metformin may cause lactic acidosis, mainly in subjects with severe renal insufficiency. Another potential problem arising from the use of metformin is the reduction in the drug's efficiency as diabetes progresses. Metformin is highly efficient when there is enough insulin production; however, when diabetes reaches the state of failure of β-cells and resulting in a type 1 phenotype, metformin loses its efficacy.

Metformin can cause vitamin B12 and folic acid deficiency. This needs to be monitored, especially in elderly patients. Though very rare, in patients with metformin intolerance or contraindications, an initial drug from other oral classes may be used. Although trials have compared dual therapy with metformin alone, few directly compare drugs as add-on therapy. A comparative effectiveness meta-analysis suggests that overall each new class of non-insulin medications introduced in addition to the initial therapy lowers A1C around 0.9–1.1%. An ongoing Glycemia Reduction Approaches in Diabetes: A Comparative Effectiveness Study (GRADE) has

compared the effect of four major drug classes (sulfonylurea, DPP-4 inhibitor, GLP-1 analog, and basal insulin) over 4 years on glycemic control and other psychosocial, medical, and health economic outcomes. Though it will be a welcome development for introduction of oral agents for metformin for gestational diabetes, current FDA regulations do not support it. [5, Rank 5]

SGLT2 (Sodium-Glucose Co Transporter 2) Inhibitors

Sodium-glucose cotransporter inhibitors are new classes of glucosuric agents: canagliflozin, dapagliflozin, and empagliflozin. SGLT2 inhibitors provide insulin-independent glucose lowering by blocking glucose reabsorption in the proximal renal tubule by inhibiting SGLT2. Because of glucose-independent mechanism of action, these drugs may be effective in advanced stages of Type 2 Diabetes Mellitus when pancreatic β-cell reserves are permanently lost. These drugs provide modest weight loss and blood pressure reduction.

Urinary tract infections leading to urosepsis and pyelonephritis, as well as genital mycosis, may occur with SGLT2 inhibitors.

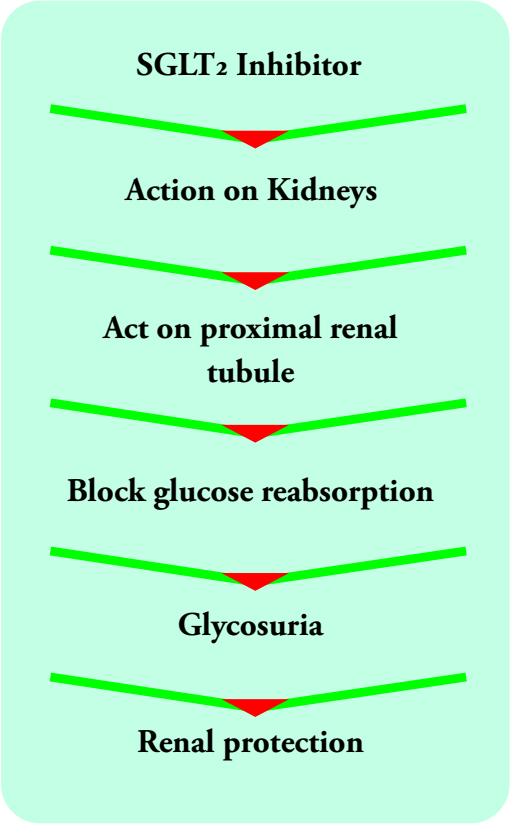

Figure 6: Action of Sodium-Glucose Co Transporter 2 Inhibitors

> **" SGLT2 inhibitors provide insulin-independent glucose lowering by blocking glucose reabsorption in the proximal renal tubule by inhibiting SGLT2. They act by inhibiting sodium-glucose transport protein 2 (SGLT2). Available drugs are canagliflozin, dapagliflozin, and empagliflozin. "**

SGLT2 inhibitors may rarely cause ketoacidosis. Patients should stop taking their SGLT2 inhibitor and seek medical attention immediately if they have symptoms of ketoacidosis (frank nausea or vomiting, or even non-specific features like tiredness or abdominal discomfort). [7, Rank 4]

They are the newest drug class for oral diabetic agents. Sodium glucose cotransporter 2 inhibitors prevent the reabsorption of renal-filtered glucose levels, resulting in decreased blood glucose levels. sodium glucose cotransporter 2 inhibitors can be used as a monotherapy or dual and triple therapy for Type 2 DM patients to moderately lower A1C levels (0.5%–1.0%).Further, SGLT2 inhibitors have the added benefits of weight loss and improved blood pressure and lipid parameters. Sodium glucose cotransporter 2 inhibitors are generally well tolerated among diabetic patients. Common adverse events include urinary tract infections, genital mycotic infections, hypotension/volume depletion, lipid alterations, hypoglycemia, and renal insufficiency. The efficacy and safety of sodium glucose cotransporter 2 inhibitors in elderly patients is consistent with younger patients; however, additional long-term studies are needed. Thus, the risks and benefits of sodium glucose cotransporter 2 inhibitors should be assessed in older patients on a case-by-case basis given the newness of the drug class.

Insulin

The clinical picture of Type 2 Diabetes Mellitus and its therapies should be regularly and objectively elaborated to patients. Many subjects with Type 2 Diabetes Mellitus shall require insulin therapy sometime during the course of the disease. For patients with Type 2 Diabetes Mellitus with inadequate target glycemic goals, insulin therapy should not be postponed. Providers should advocate insulin as a therapy in a complete non-judgmental, empathetic, and non-punitive approach to ensure superior quality of adherence. Self-monitoring of blood glucose (SMBG) contributes to significant improvement of glycemic control in patients with Type 2 Diabetes Mellitus initiating insulin. Close and frequent monitoring of the patient is needed for any dose titration to achieve target glycemic goals, as well as to prevent hypoglycemia.

“ If non-insulin monotherapy like metformin at the maximum tolerated dose does not achieve or maintain the A1C target over 3 months, then a second oral agent may be added to the regimen, a GLP-1 receptor agonist or basal insulin. Insulin therapy with or without additional agents should be introduced in patients with newly identified T2DM and frankly symptomatic (catabolic features like weight loss, ketosis or features of hyperglycemia including polyuria/polydipsia) and/or severely elevated blood glucose levels [≥ 300–350 mg/dL (16.7–19.4 mmol/L)] or A1C [≥10–12%]. ”

Basal insulin

It is the initial insulin regimen, beginning at 10U or 0.1–0.2U/kg, depending on the hyperglycemia severity (titrating by 2–3 U every 4–7days till glycemic goal is reached). Use of basal insulin greater than 0.5 U/kg indicates the need for use of an additional agent. Basal insulin is usually added to oral metformin and possibly one additional non-insulin agent like DPP-4 or SGLT-2 inhibitor.

NPH (Neutral Protamine Hagedorn) insulin

It carries low risk of hypoglycemia in individuals without any significant past history, and is low cost. Newer, longer acting, basal insulin analogs have superior pharmacodynamic profiles, delayed onset and longer duration of action but low risk of hypoglycemia, albeit at higher costs. Concentrated basal insulin preparations such as U-500 regular are five times more potent per volume of insulin (i.e., 0.01 mL ~5 U of U-100 regular) than U-100 regular. U-300 glargine and U-200 degludec are other potent, ultra-long acting preparations.

If basal insulin contributes to acceptable fasting blood glucose, but A1C persistently remains above target, mealtime insulin may be added. Rapid-acting insulin analog (lispro, aspart, or glulisine) may be used and administered just before meals. The glucose levels should be monitored before meals and after the injections.

Another approach to control the periprandial glucose excursions may be to add twice-daily premixed (or biphasic) insulin analogs (70/30 aspart mix, 75/25 or 50/50 lispro mix). The total present insulin dose may be computed and then one-half of this amount may be administered as basal and the other half during mealtime, the latter split equally between three meals. Regular human insulin and human NPH–Regular premixed formulations (70/30) are less expensive alternatives to rapid-acting insulin analogs and premixed insulin analogs, respectively, but their unpredictable pharmacodynamic profiles make them inadequate to cover postprandial glucose changes.

Sometime, bolus insulin needs to be administered in addition to basal insulin. Rapid-acting analogs are used as bolus formulations due to their prompt onset of action. Insulin pump (continuous subcutaneous insulin infusion) may be used instead to avoid multiple injections. Often, patients and physicians are reluctant to intensify therapy due to the fear of hypoglycemia, regimen complexity, and increased multiple daily injections. There is a need for a flexible, alternative intensification option taking into account individual patient considera-

tions to achieve or maintain individual glycemic targets. An ideal insulin regimen should mimic physiological insulin release while providing optimal glycemic control with low risk of hypoglycemia, weight gain, and fewer daily injections.

During insulin therapy, sulfonylureas, DPP-4 inhibitors, and GLP-1 receptor agonists are stopped once more complex insulin regimens beyond basal insulin are used. In patients with inadequate blood glucose control, especially if requiring escalating insulin doses, Thiazolidinediones usually pioglitazone or SGLT2 inhibitors may be added as adjunctive therapy to insulin.

Insulin injections can cause weight gain or loss. Insulin drives potassium into the cell and can cause hypokalemia. Components of the insulin preparation have the potential to cause allergy. Insulin injections, along with the use of other drugs like Thiazolidinediones (TZDs), can precipitate cardiac failure.

Stressful events like illness, surgery, and trauma can impede glycemic control and may lead to development of diabetes keto acidosis or non-ketotic hyperosmolar state, life-threatening conditions which merit immediate medical attention. Any condition that deteriorates glycemic control necessitates more frequent monitoring of blood glucose in an inpatient setting; ketosis-prone patients also require urine or blood ketone monitoring. If accompanied by ketosis, vomiting, or altered mental status, marked hyperglycemia requires hospital admission. The patient treated with non-insulin therapies or medical nutrition therapy alone may require insulin. Patient must be aggressively hydrated and infections should be controlled.

“ Inhaled insulin is now available for prandial use. However, the dosing range is limited. Use of inhaled insulin requires pulmonary function testing prior to and after starting therapy. It is contraindicated in subjects with asthma or other lung diseases. ”

Without adequate treatment, prolonged hyperglycemia can cause glucose toxicity that can progressively impair insulin secretion. Initiation of insulin therapy is critical to reverse the toxic effect of high blood glucose levels on the pancreas. Once persistent glycemic control is achieved, insulin can be tapered off and replaced with oral medications. At some point in the management of Type 2 Diabetes Mellitus, β-cell reserves are exhausted, with phenotypic reversal to a Type 1 DM kind of pathophysiological situation. Meticulous follow-up may identify such states and then the need for continued reliance on insulin

therapy may be carefully explained to the patients.

Weight gain can raise a barrier to the use of insulin in Type 2 Diabetes Mellitus. In the United Kingdom Prospective Diabetes Study (UKPDS) study, patients gained 6 kg with insulin therapy, when compared with 1.7–2.6 kg weight gain with sulfonylureas. More recently, the combination of GLP-1 receptor agonists and insulin has been useful in tackling the weight gain associated with insulin and circumventing the need for high doses in the presence of significant insulin resistance. Lipoatrophy with insulin injections is not seen now; however, lipohypertrophy due to failure to change the subcutaneous injection sites is still a common cause of poor insulin absorption and suboptimal glycemic control.

In the Action to Control Cardiovascular Risk in Diabetes trial, aggressive treatment of Type 2 Diabetes Mellitus patients with higher cardiovascular risk was associated with higher all-cause and cardiovascular mortality. Exposure to injected insulin was hypothesized to increase cardiovascular mortality. However, after adjustment for baseline covariates, no significant association of insulin dose with cardiovascular death remained. Older patients with cognitive dysfunction may not benefit from intensive therapy. Furthermore, hypoglycemia in the elderly may cause cardiac ischemia, arrhythmia, myocardial infarction, and sudden death. [8, Rank 5]

Insulin is often underutilized in elderly patients due to concerns about hypoglycemia, misconceptions about insulin, social stigma, needle phobia, complexity of injection skills, low adaptation capacity, and, moreover, clinical inertia. Before initiating insulin therapy, comprehensive evaluation of psychosocial barriers, functional status (ie, visual acuity and manual dexterity), cognitive status, and financial ability to afford insulin and insulin-delivery supplies should be made to ensure safety, compliance, and effectiveness of insulin use.

> **“ Insulin therapy is inevitable when β-cell preservation is severely impaired due to advanced age or long-lasting Type 2 Diabetes Mellitus. Early use of insulin may reduce glucotoxicity and restore function of β-cells. ”**

Conventional neutral protamine Hagedorn (NPH) insulin and regular insulin were not recommended due to variable bioavailability and nonphysiological pharmacokinetics that put patients in higher risk of hypoglycemia. Long-acting insulins degludec, glargine, and detemir are safer choices than NPH in older adults because

of their lower risk of hypoglycemia, especially nocturnal hypoglycemia, which may contribute to cardiovascular morbidity and falls. Insulin degludec resulted in less hypoglycemia than insulin glargine even in long-duration diabetic patients, whose counterregulatory hormone responses were presumed to be weaker. Besides, insulin analogs are mostly delivered through insulin pens, which leads to improved adherence, accuracy of injection, quality of life, and decreased admissions for hypoglycemia.

For elderly diabetic patients with inadequately controlled hyperglycemia, patients with early combinations of basal insulin had better glycemic control and less hypoglycemia than titration of oral antidiabetic drugs. In diabetic elders with poorly controlled glycemia, insulin therapy did not result in higher hypoglycemia events if glycemic targets were less stringent. A once-daily insulin regimen was also more preferred by an older population than more frequent dosing. Prandial insulin supplement in basal bolus regimen or premixed insulin may be appropriate in highly selected elderly patients with good functional reserve. Judicious use of insulin as an add-on therapy may improve mental health, quality of life, social functioning, treatment satisfaction, and caregiver strain in elderly diabetic patients with poor glycemic control.

Sulfonylureas

They are divided into two groups (as shown in Figure 7)

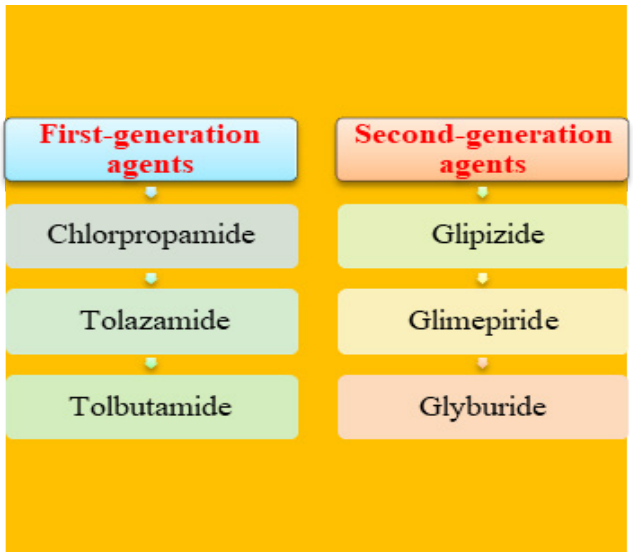

Figure 7: Classification of Sulfonylureas

Sulfonylureas lower blood glucose level by increasing insulin secretion in the pancreas by blocking the KATP channels. They also limit gluconeogenesis in the liver. (as shown in Figure 8)

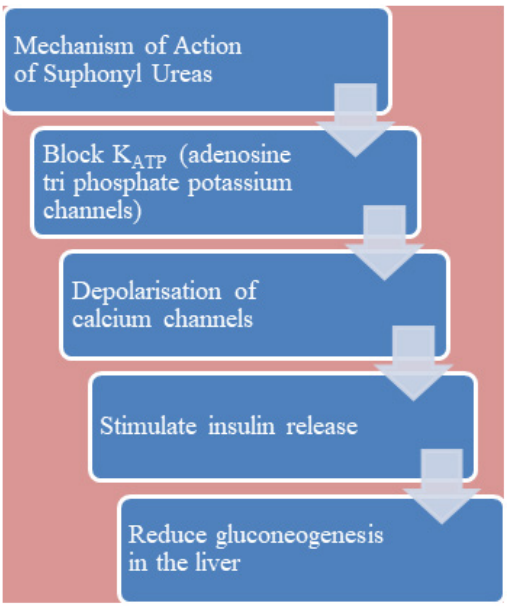

Figure 8: Action of Sulphonyl ureas

Sulfonylureas decrease breakdown of lipids to fatty acids and reduce clearance of insulin in the liver. Sulfonylureas are currently prescribed as second-line or add-on treatment options for management of Type 2 Diabetes Mellitus. The first-generation sulfonylureas are known to have longer half-lives, higher risk of hypoglycemia, and slower onset of action, as compared to second-generation sulfonylureas. Currently, in clinical practice, second-generation sulfonylureas are prescribed and more preferred over first-generation agents because they are proven to be more potent given to patients at lower doses with less frequency , with the safest profile being that of glimepiride.

Drugs that can prolong the effect of sulfonylureas such as aspirin, allopurinol, sulfonamides, and fibrates must be used with caution to avoid hypoglycemia. Moreover, other oral antidiabetic medications or insulin can be used in combination with sulfonylurea and can substantially increase the risk of hypoglycemia.

" Hypoglycemia is the major side effect of all sulfonylureas, while minor side effects such as headache, dizziness, nausea, hypersensitivity reactions, and weight gain are also common. They are contraindicated in patients with hepatic and renal diseases and are also contraindicated in pregnant patients due to the possible prolonged hypoglycemic effect to infants. "

Patients on beta-adrenergic antagonists for the management of hypertension can have hypoglycemia unawareness. Sulfonylureas should be used with caution in subjects receiving beta blockers. [9, Rank 3]

Insulin secretagogues, which stimulate insulin release from pancreatic β-cells, have been popular for a long time because of their good efficacy and relatively low cost. As pancreatic β-cell function decreases with aging, insulin secretagogues are theoretically a good choice to enhance insulin secretion in older adults. Risk of hypoglycemia among elderly patients treated with sulfonylureas (SU), especially glyburide (glibenclamide) and chlorpropamide, is higher than among younger adults, which is associated with more hypoglycemia-related hospitalizations. Higher risk of hypoglycemia related to sulfonylureas use is associated with impaired renal function, impaired hepatic function, recent hospitalization, polypharmacy, alcohol use, and caloric restriction in older adults. Sensitivity to sulfonylureas may increase, especially in those aged over 80, which makes the oldest-old more vulnerable to hypoglycemia. Despite these drawbacks, there is no need to abruptly withdraw sulfonylureas from all older

adults. Its once-daily dosage form is potentially good for improving compliance of older adults and for minimizing dosing errors. Guidelines developed all over the world suggest avoidance of only glyburide in older adults, which was associated with the most long-lasting, life-threatening hypoglycemic events. The most important thing in prescribing sulfonylureas in older adults is to follow the principle of starting SU from lowest dose, to slowly titrate to the individualized target, and to closely monitor any hypoglycemia symptoms, especially in elderly patients whose pancreatic β-cell function is only mildly impaired. sulfonylureas s may still fail to be effective in some patients, as they develop pancreatic β-cell failure, especially in elderly patients with long-lasting diabetes, which makes it an appropriate substitute for insulin in patients whose glycemic targets are not stringent. [13, Rank 5]

Meglitinide

Meglitinides (repaglinide and nateglinide) are non-sulfonylurea secretagogues, which was approved as treatment for type 2 DM. The meglitinides are rapid-acting insulin secretagogues with a short duration of action, and are aimed at increasing prandial insulin secretion.

Meglitinide shares the same mechanism as that of sulfonylureas; it also binds to the sulfonylurea receptor in β-cells of the pancreas. However, the binding of meglitinide to the receptor is weaker than sulfonylurea, and thus considered short-acting insulin secretagogues, which gives flexibility in its administration. Also, a higher blood sugar level is needed before it can stimulate β-cells' insulin secretion, making it less effective than sulfonylurea. Rapid-acting secretagogues (meglitinides) may be used in lieu of sulfonylureas in patients with irregular meal schedules or those who develop late postprandial hypoglycemia while using a sulfonylurea. [10, Rank 4]

> **" Meglitinide bind to the sulphonyl urea 1 receptor on the β-cell, although with lower affinity than sulfonylureas, and stimulate insulin release in the same way. Nateglinide should not be used with suphonyl ureas because of competitive binding of suphonyl ureas receptors. "**

A randomized, open-label, crossover trial suggested that repaglinide is safe and effective with lower risk of hypoglycemia compared with suphonyl ureas in older patients with borderline poor glycemic control. Hypoglycemia is related to missed meals, so meglitinides should be taken within 30 minutes before meals. Therefore, meglitinides should be prescribed with caution in the elderly patients with cognitive

impairment and erratic eating habits. Hepatic and renal insufficiency may prolong the action of repaglinide, resulting in higher risk of hypoglycemia in these conditions. Disadvantages include relatively high cost, frequency of administration, and strict regulation of time of taking medicine, which contribute to the complexity of polypharmacy in older adults.

Thiazolidinedione

Like biguanides, Thiazolidinedione improve insulin action. Rosiglitazone and pioglitazone are representative agents. Thiazolidinedione are agonists of peroxisome proliferator-activated receptor (PPAR) and facilitate increased glucose uptake in numerous tissues including adipose, muscle, and liver. Mechanisms of action include diminution of free fatty acid accumulation, reduction in inflammatory cytokines, rising adiponectin levels, and preservation of β-cell integrity and function, all leading to improvement of insulin resistance and β-cell exhaustion. However, there are high concerns of risks overcoming the benefits. Namely, combined insulin-Thiazolidinedione therapy causes heart failure. Thus, Thiazolidinedione are not preferred as first-line or even step-up therapy. [11, Rank 5]

The Thiazolidinedionewhich are insulin sensitizers and which act through activation of peroxisome proliferator-activated receptors gamma, are effective in lowering fasting glucose level through increased peripheral insulin sensitivity, especially of muscle and adipocytes. Pioglitazone, when prescribed in patients older than 65 years, had similar effectiveness and safety as in younger adults. It was also suggested that a combination of pioglitazone and sitagliptin improved α-cell and β-cell functions, thus reducing postprandial glucose excursions more than by either treatment alone.

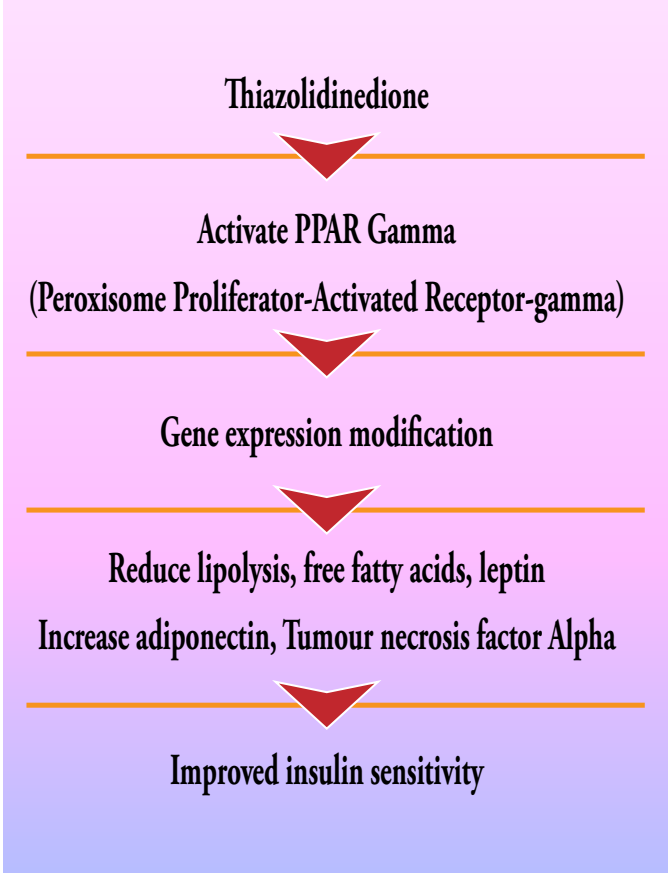

Figure 9: Action of Thiazolidinedione

Considering the low incidence of hypoglycemia of each class of the drugs, this combination seemed promising in glycemic control for older adults. However, safety profiles of Thiazolidinedione are still a con-

cern. It should not be used in patients with active liver disease. Increased rates of bone fractures was observed in elderly women taking rosiglitazone but not in men from the A Diabetes Outcome Progression Trial (ADOPT). However, increased fractures were observed at the humerus, hand, and foot, rather than the typical osteoporotic sites. A similar finding was also found in the PRO active trial. The effect of pioglitazone on bone mineral density is reported as a trend of decrease in proximal femur, hip, and lumbar spine in diabetic women, but no effect in prediabetic women. There were no changes in biochemical markers of bone turnover. As the clinical and pathophysiological evidence still advises the association between Thiazolidinedione and fractures, its application in older adults should be made with caution.

Another concern is its effect on cognition. As reported in the ACCORD-MIND cohort, exposure to rosiglitazone is associated with greater decline in cognitive performance compared with insulin therapy. Despite the current evidence against the use of rosiglitazone in Alzheimer's disease (AD), pioglitazone exhibited cognitive and functional improvement in mild AD. More evidence is needed to make recommendations about the use of pioglitazone in AD.

Thiazolidinedione are also related to fluid retention. When used in patients with diabetic macular edema, worsening of the condition was reported. Current evidence suggests that Thiazolidinedione could still be safely continued in patients without macular edema. However, this feature limits its application in patients with class III or IV congestive heart failure. The risk of ischemic stroke, myocardial ischemia, and heart failure is still inconclusive in rosiglitazone and pioglitazone. Prescription of rosiglitazone in some areas is highly restricted now.

Despite the positive effect of Thiazolidinedione on glycemic control, lean body mass, cognition, and low risk of hypoglycemia, drawbacks such as increased risk of fractures, probable macular edema, heart failure, and fluid retention exist. Application of Thiazolidinedione in older diabetic adults needs to be carefully evaluated for its risk/benefit ratio.

" Newer generation Thiazolidinedione, termed as selective peroxisome proliferator-activated receptors gamma modulators, which may minimize the unwanted effects of current Thiazolidinedione, are being developed and may be promising in the future. "

Alpha-glucosidase inhibitors (AGI)

They are widely used in the treatment of patients with type 2 diabetes. Alpha-glucosidase inhibitors delay the absorption of carbohydrates from the small intestine and thus have a lowering effect on postprandial blood glucose and insulin levels. Examples are acarbose, miglitol, voglibose.

Alpha-glucosidase inhibitors slow down digestion by blocking enzymes in the small intestine that break down carbohydrates. By blocking these enzymes, the medication can slow down the digestion of carbohydrates in the small intestine so that glucose from food enters the bloodstream more slowly, thus reducing the rise in blood glucose levels after eating.

Alpha-glucosidase inhibitors (AGIs) delay absorption of carbohydrates and result in decreased postprandial glucose excursions, improvement of glycemic variability without increased oxidative stress, and possible improvement of β-cell response. Maximal antihyperglycemia is achieved with lower doses (25 mg before meals) in elderly patients than their younger counterparts. Moreover, Alpha-glucosidase inhibitors may increase insulin sensitivity in diabetic elderly patients. They are effective in elderly overweight type 2 diabetic patients. They are well tolerated in older adults even with multiple comorbidities with a low incidence of hypoglycemia as monotherapy. Alpha-glucosidase inhibitors also reduced the risk of postprandial hypoglycemia and late hypoglycemia in older adults with T2DM who eat rice porridge as main meal, due to impaired chewing function. When hypoglycemia occurs in regimens combined with Alpha-glucosidase inhibitors it should be treated with oral glucose because other complex carbohydrates will not relieve the event. Special education should be imparted to the elderly patients and their family members to manage such hypoglycemic conditions. Further, if Alpha-glucosidase inhibitors are prescribed with prandial insulin, mismatch between peak serum glucose levels and peak prandial insulin levels may occur, placing patients at increased risk for hypoglycemia. The most common adverse events are gastrointestinal disturbances, especially flatulence, abdominal distension, diarrhea, abdominal pain, and abdominal discomfort, which preclude AGIs application in the elderly patients. The clinical response of Alpha-glucosidase inhibitors depends on preserved β-cell function. That is, Alpha-glucosidase inhibitors are more effective in newly diagnosed diabetes and less effective in long-standing diabetes with severely impaired insulin secretion. Another concern is that Alpha-glucosidase inhibitors should be taken with meals, which increases the complexity of the medication regimen and may lead to nonadherence. [14, Rank 4]

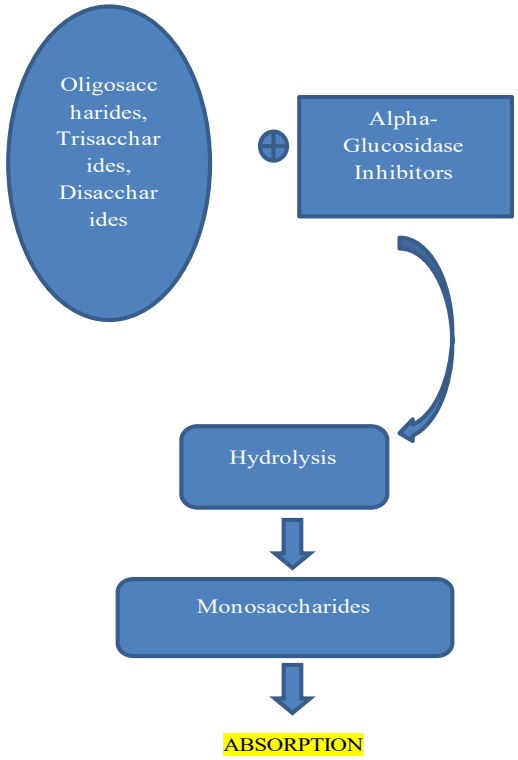

Figure 10: Action of Alpha-Glucosidase inhibitors

" The membrane-bound intestinal alpha-glucosidases hydrolyze oligosaccharides, trisaccharides, and disaccharides to glucose and other monosaccharides in the small intestine. Acarbose also blocks pancreatic alpha-amylase in addition to inhibiting membrane-bound alpha-glucosidases. "

Incretin Mimetics

They are the Glucagonlike peptide–1 (GLP-1) agonists and Dipeptidyl peptidase 4 inhibitors

Incretin effect is the difference in insulin secretory response from an oral glucose load in comparison to glucose administered intravenously. The incretin effect is responsible for 50–70% of total insulin secretion after oral glucose intake. The two naturally occurring incretin hormones that play important roles in the maintenance of glycemic control: glucose-dependent insulinotropic polypeptide (GIP, or incretin) and glucagon-like peptide (GLP-1); these peptides have a short half-life, as these are rapidly hydrolyzed by DPP-4 inhibitors within 1½ min. In patients with Type 2 Diabetes Mellitus, the incretin effect is reduced or absent. In particular, the insulinotropic action of GIP is lost in patients with Type 2 Diabetes Mellitus. Incretins decrease gastric emptying and causes weight loss. Because of impact on weight loss, these medications may find increasing use in diabesity.

" Drugs in the incretin mimetic class include exenatide (Byetta, Bydureon), liraglutide (Victoza), sitagliptin (Januvia, Janumet, Janumet XR, Juvisync), saxagliptin (Onglyza, Kombiglyze XR), alogliptin (Nesina, Kazano, Oseni), and linagliptin (Tradjenta, Jentadueto). "

Targeting the incretin system has become an important therapeutic approach for treating Type 2 Diabetes Mellitus. These

two drug classes include GLP-1 receptor agonists and DPP-4 inhibitors. Clinical data have revealed that these therapies improve glycemic control while reducing body weight (specifically, GLP-1 receptor agonists) and systolic blood pressure in patients with Type 2 Diabetes Mellitus. Furthermore, hypoglycemia is low (except when used in combination with a sulfonylurea) because of their glucose-dependent mechanism of action.

Incretin-based therapies have drawn increasing attention in recent years because of their properties of enhancing glucose-dependent insulin secretion after ingestion of food. Both GLP-1 and glucose-dependent insulinotropic peptide are degraded rapidly by DPP4, resulting in short plasma half-lives. GLP-1 suppresses glucagon secretion, delays gastric emptying, increases satiety, and decreases food intake. There are two classes of drugs focusing on incretin effect, namely, DPP4 inhibitors and GLP-1 receptor agonists.

GLP-1 (Glucagonlike peptide–1)

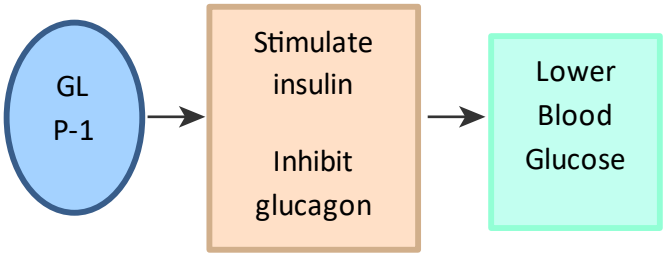

Figure 11: Effect of GLP-1 Receptor Agonists

Receptor Agonists

The currently GLP-1 receptor agonists available are exenatide and liraglutide. These drugs exhibit increased resistance to enzymatic degradation by DPP4. In young patients with recent diagnosis of Type 2 Diabetes Mellitus, central obesity, and abnormal metabolic profile, one should consider treatment with GLP-1 analogs that would have a beneficial effect on weight loss and improve the metabolic dysfunction. GLP-1 analogs are contraindicated in renal failure.

Exenatide

Exenatide, an exendin-4 mimetic with 53% sequence homology to native GLP-1, is currently approved for Type 2 Diabetes Mellitus treatment as a single drug in the US and in combination with metformin±sulfonylurea. Because of its half-life of 2.4 h, exenatide is advised for twice-daily dosing. Treatment with 10 μg exenatide, as an add-on to metformin, resulted in significant weight loss (–2.8 kg) in comparison to patients previously treated with metformin alone. Exenatide is generally well tolerated, with mild-to-moderate gastrointestinal effects being the most common adverse effect.

This drug class acts on the GLP-1 receptor directly with long duration due to its resistance to degradation by DPP. GLP-1

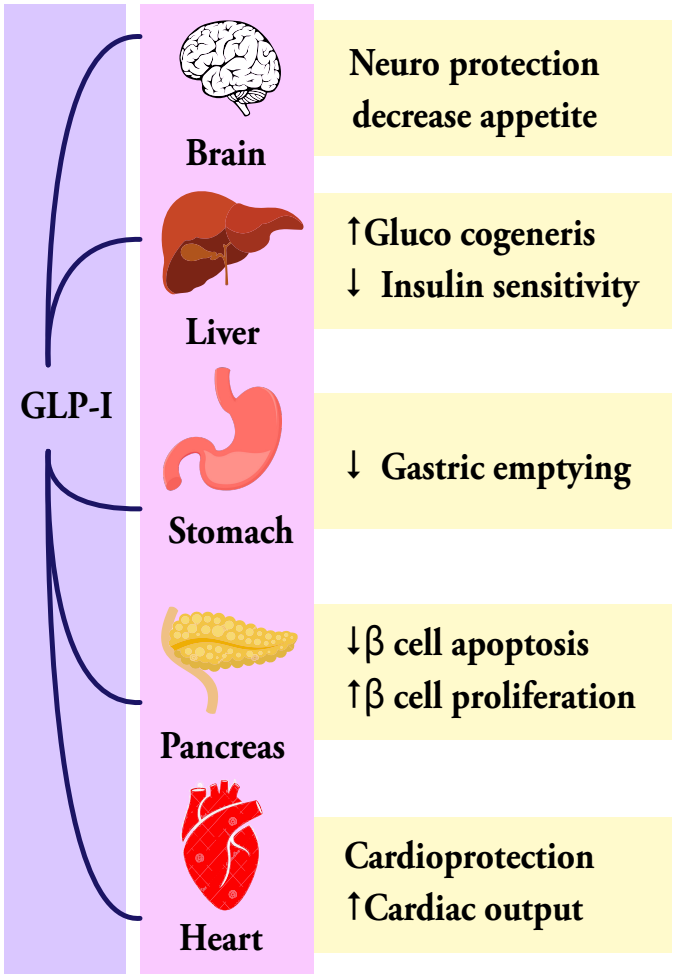

Figure 12: Actions of GLP 1 Agonists

receptor agonists are effective in glycemic control and are well tolerated without increasing the risk of hypoglycemia in older patients. In addition to their glucose-lowering effects, GLP-1 receptor agonists delay gastric emptying and increase satiety, resulting in weight loss, in particular reductions in subcutaneous fat mass. Liraglutide also resulted in slight reductions of visceral fat mass in pioglitazone users. Both liraglutide and exenatide ameliorate concomitant nonalcoholic fatty liver disease. The evidence of their impact on muscle mass is still lacking. However, just as the concern in DPP4 inhibitors, the effect of GLP-1 receptor agonists on A1C reductions was also inversely related to diabetes duration, ie, to the preservation of β-cell function. Thus, the characteristics of GLP-1 receptor agonists might be beneficial to obese diabetic elders if used early in the course of diabetes. However, their weight-reducing effect and gastrointestinal side effects may be detrimental for the frail elderly patients with poor caloric intake and poor nutrition status. These drugs should be used with caution in diabetic elders who are undergoing unintentional weight loss, and who are malnourished or at high risk for malnutrition. Metabolism and excretion of liraglutide is not affected by renal impairment, even in patients with end-stage renal disease. Recommendations for use of liraglutide in patients with more advanced renal impairment are limited. Exenatide is excreted through the kidney, and is not recommended for use in severe renal impairment or end-stage renal disease.

Liraglutide

Liraglutide is a GLP-1 analog that shares 97% sequence identity to native GLP-1. Liraglutide has a long duration of action (24h). Liraglutide causes 1.5% decrease in A1C in individuals with type 2 diabetes, when used as monotherapy or in combination with one or more selected oral

antidiabetic drugs. Liraglutide decreases body weight; the greatest weight loss resulted from treatment with liraglutide in combination with combined metformin/sulfonylurea (–3.24 kg with 1.8 mg liraglutide). Liraglutide also diminishes systolic pressure (mean decrease –2.1 to –6.7 mmHg). Liraglutide is well tolerated, with only nausea and minor hypoglycemia

Metformin is generally the recommended first-line oral anti-hyperglycaemic agent for type 2 diabetes therapy; it is considered weight neutral and to be associated with a low risk of hypoglycaemia. If glycaemic control is not achieved with monotherapy, two- and then three-drug combination therapy may be implemented, commonly involving metformin, sulphonylureas, thiazolidinediones, glucagon-like peptide-1 (GLP-1) receptor agonists, dipeptidyl peptidase-4 (DPP-4) inhibitors and insulin. Insulin therapy is generally initiated with basal insulin, and rapid insulin analogues prescribed if postprandial glucose control is required. In all cases, anti-hyperglycaemic agents should be selected on a patient-specific basis, dependent on the benefit-to-risk profile of patients to minimise unwanted effects.

The GLP-1 receptor agonists constitute a well-established group of therapeutics for type 2 diabetes that promote glucose-dependent insulin secretion and inhibit glucagon release. Predominant in clinical use is the GLP-1 receptor agonist liraglutide which has demonstrated high levels of glycaemic benefit in head-to-head studies vs. other GLP-1 receptor agonists.

Liraglutide was extensively studied in the Liraglutide Effect and Action in Diabetes (LEAD) phase III trial programme. In these studies, liraglutide was associated with clinically significant reductions in glycated haemoglobin (HbA1c) of 0.8–1.5 %, whether given as monotherapy or as combination therapy with metformin, glimepiride, rosiglitazone or insulin. Liraglutide also has several other clinical benefits, including reductions in body weight and systolic blood pressure and low rates of hypoglycaemia.

Liraglutide is dosed once daily using a prefilled pen. Treatment is initiated at 0.6 mg per day for 1 week. This initial dose is intended to reduce gastrointestinal symptoms. After 1 week, the dose is increased to 1.2 mg, and can be further increased to 1.8 mg based on individual glycaemic control.
Among the large number of clinical pharmacology studies published on liraglutide, this updated review has prioritised, where available, the most recent studies conducted in subjects with type 2 diabetes and those using the recommended treatment doses of 1.2 and 1.8 mg. When relevant and for completeness, studies in other populations

> **"Liraglutide is an acylated human GLP-1 analogue, with 97 % amino acid homology to native GLP-1. GLP-1 enhances meal-induced insulin secretion, the so-called 'incretin effect', and has several other actions that are desirable for an anti-diabetic agent. However, although intravenous infusion of native GLP-1 can normalise plasma glucose levels in patients with type 2 diabetes,"**

or using lower liraglutide doses are included.

Liraglutide is not a practical option for exogenous therapy. This is because of its very short half-life (t½) [<2 min following intravenous administration], as a result of rapid degradation by the enzymes DPP-4 and neutral endopeptidase (NEP), as well as efficient clearance by the kidneys.

Liraglutide differs from the native compound by acylation of the lysine residue at position 26 with a hexadecanoyl-glutamyl side chain, and a single lysine-to-arginine amino acid substitution at position 34. Possibly because of the high level of amino acid homology to native GLP-1, liraglutide has low immunogenicity. However, the subtle differences in sequence compared with native GLP-1, as well as the acylation, lead to a greatly protracted action profile. Following injection, liraglutide is highly non-covalently bound to the dominant plasma protein, human serum albumin (>99 % in vitro), which is most likely via a fatty acid-binding site. The following main mechanisms underlie the protraction of liraglutide: (1) slowed absorption following subcutaneous injection; and (2) reduced elimination rate owing to slowed metabolism and renal filtration. [17, Rank 5]

The pharmacokinetics of liraglutide has been evaluated in several single- and multiple-dose clinical pharmacology trials. To support the pharmacokinetic evaluation, sparse sampling for liraglutide assay was taken in two phase III studies that included patients with type 2 diabetes: one trial conducted in America, primarily including USA sites with doses of 1.2 and 1.8 mg and one trial conducted in Asia with doses of 0.6, 1.2 and 1.8 mg.

Liraglutide Assay

A validated two-site enzyme-linked immunosorbent assay has been developed, using two monoclonal antibodies directed against different liraglutide epitopes. The two antibodies used for the assay are directed against the N- and C-terminal regions of the liraglutide molecule, respectively. The lower limit of quantification was initially 30 pM, and was later reduced to 18 pM. Cross-reactivity with endogenous GLP-1 has been eliminated.

Absorption, Distribution, Metabolism and Excretion

Studies in healthy subjects and in patients with type 2 diabetes have demonstrated that the pharmacokinetic properties of liraglutide make it suitable for once-daily dosing. Across studies and populations, liraglutide has shown to be slowly absorbed following subcutaneous injection, with a tmax of approximately 12 h (range 7–14 h), and an absolute bioavailability of around 55 %. The plasma t½ has been estimated at approximately 13 h (range 11–15 h). In healthy subjects, with multiple doses up to 12.5 µg/kg (~0.9 mg) daily, steady state was reached after approximately 3 days, with a mean accumulation ratio of 1.4–1.5.

Estimates of clearance and volume of distribution ranged from 0.6 to 1.2 L/h and from 11.0 to 24.7 L, respectively, and were consistent across populations: healthy/type 2 diabetes, race groups, age groups, injection sites and dose levels. The relatively small volume of distribution suggests that liraglutide is mainly distributed in the intravascular fluid and extracellular compartment, which aligns with its high degree of albumin binding.

Based on data from a population pharmacokinetic analysis in subjects with type 2 diabetes, the inter-patient variability of clearance has been estimated at 36 %, without accounting for demographic covariates; this was reduced to 28 % after correcting for differences in body weight and sex (the two most important covariates).

The effect of the site of injection (abdomen, upper arm or thigh) on the pharmacokinetic profile of liraglutide has been investigated in healthy subjects. Bioavailability was found to be equivalent in comparisons of upper arm vs. both abdomen and thigh, but slightly lower with administration in the thigh compared with the abdomen. However, this minor difference was not considered to be clinically relevant. In clinical practice, administration of liraglutide can be interchanged between the three sites without dose adjustment.

The metabolism of liraglutide appears to follow a similar pathway to native GLP-1 with cleavage by DPP-4 and NEP into several metabolites. In a study with radiolabelled liraglutide, no intact liraglutide was excreted in urine or faeces, and low levels of metabolites were detected in plasma, indicating that the drug is completely degraded into peptides, amino acids and fatty acid fragments within the body. [18, Rank 1]

Being a protein, liraglutide has low potential for interactions with drugs cleared by cytochrome P450. This has been confirmed in non-clinical in vitro and in vivo studies. The underlying protraction and clearance mechanisms of liraglutide also give rise to a low potential for drug–drug interaction.

In vitro studies in human plasma showed that liraglutide protein binding was not changed in the presence of a number of highly protein-bound drugs. Furthermore, therapeutic plasma concentrations of liraglutide are relatively low (up to 25–50 nM) compared with plasma albumin concentrations (typically around 500–700 μM in humans), and hence it is unlikely that liraglutide will alter the protein binding of other drugs. The binding of liraglutide to albumin is most likely via the fatty acid-binding sites.

As a result of the above information, clinical investigations of liraglutide drug–drug interactions have focussed primarily on the slowed gastric emptying with liraglutide, which may affect the absorption of concomitantly administered oral drugs. The selected drugs represent a range of drugs of different solubilities and permeabilities including all four classes (I–IV) in the Biopharmaceutics Classification System. These studies have shown minor effects on overall exposure but delayed initial absorption of a variety of concurrent oral medications such as paracetamol, atorvastatin, griseofulvin, digoxin, lisinopril and an oral combination contraceptive. These effects were not considered to be clinically relevant and dose adjustments for co-administered drugs are not required.

GLP-1 analogues are often used in combination with insulin products, and liraglutide in combination with insulin detemir and insulin degludec has been shown to provide good glycaemic control, sustained weight loss and low rates of hypoglycaemia.

An interaction study was conducted to investigate potential pharmacokinetic and pharmacodynamic interactions between liraglutide and insulin detemir when administered together. Co-administration of liraglutide 1.8 mg (at steady state) and insulin detemir (single dose) in patients with type 2 diabetes produced an additive glucose-lowering effect without affecting the pharmacokinetic profile of either agent (as evaluated by AUC, Cmax and tmax). This suggests that the addition of insulin detemir in patients already being treated with liraglutide does not require a different insulin titration algorithm from that used when combined with oral anti-diabetic agents. This is in agreement with the different clearance mechanisms of insulins and GLP-1 analogues.

Using a fixed-dose combination of liraglutide and insulin degludec with preserved pharmacokinetic properties of the two active components, treatment benefits were seen across the entire dose and exposure range compared with each component dosed alone. [19, Rank 1]

DPP-4 Inhibitors

Dipeptidyl peptidase 4 inhibitors include sitagliptin, saxagliptin, vidagliptin, linagliptin, and alogliptin. These medications may be used as single therapy, or in addition with metformin, sulfonylurea, or TZD. This treatment is similar to the other oral antidiabetic drugs. The gliptins have not been reported to cause higher incidence of hypoglycemic events compared with controls. Dipeptidyl peptidase 4 inhibitors impact postprandial lipid levels. Treatment with vidagliptin for 4 weeks decreases postprandial plasma triglyceride and apolipoprotein B-48-containing triglyceride-rich lipoprotein particle metabolism after a fat-rich meal in Type 2 Diabetes Mellituspatients who have previously not been exposed to these medications. In diabetic patients with coronary heart disease, it was demonstrated that treatment with sitagliptin improved cardiac function and coronary artery perfusion.

The three most commonly reported adverse reactions in clinical trials with gliptins were nasopharyngitis, upper respiratory tract infection, and headache. Acute pancreatitis was reported in a fraction of subjects taking sitagliptin or metformin and sitagliptin. An increased incidence of hypoglycemia was observed in the sulfonylurea treatment group.

In the elderly, DPP-4 inhibitors lower blood glucose but have minimal effect on caloric intake and therefore less catabolic effect on muscle and total body protein mass. In decreased doses, DPP-4 inhibitors are considered safe in patients with moderate to severe renal failure. [6, Rank 3]

This drug class inhibits DPP4, and thus prolongs the action of GLP-1 and glucose-dependent insulinotropic peptide in diabetic patients whose incretin response is impaired. Among the currently available DPP4 inhibitors, sitagliptin, vildagliptin, saxagliptin, linagliptin, and alogliptin have been confirmed to be well tolerated in older adults with few gastrointestinal side effects and little effect on BW, with similar efficacy as younger adults, and can be safely used in renal insufficiency with labeled dose adjustment for each drug. DPP4 inhibitors resulted in reductions in A1C for patients whose baseline A1C levels were higher. These excellent tolerability profiles, low risk of hypoglycemia, and once-daily dosing make this drug class suitable for frail and debilitated elderly patients.

DPP4 inhibitors enhance the effect of insulin secretion stimulated by SU, and thus increase the risk of hypoglycemia when used in combinations with SU. This characteristic also indicates that DPP4 inhibitors are efficacious with preserved β-cell insulin secretion, and may be primarily effective

early in the course of diabetes with mild hyperglycemia. Conversely, DPP4 inhibitors might be ineffective in elderly patients with long-lasting T2DM and poorly preserved β-cell insulin secretion.

Bile acid sequestrants

Colesevelam hydrochloride was originally approved for treatment of hyperlipidemia; however, subsequent clinical trials demonstrated an improvement in glycemia for patients with type 2 diabetes mellitus. Colesevelam is a bile acid sequestrant designed to have a high affinity and capacity for binding to bile acids. Colesevelam is nonabsorbable by the body, and its distribution is confined to the digestive tract. Its hydrophilic and water-insoluble nature facilitates binding of bile acids in the intestine and excretion of these complexes in the feces. As a result, the body increases the conversion of cholesterol to bile acids, resulting in an uptake of low-density lipoprotein cholesterol (LDL-C) by the liver to the blood, thereby lowering serum LDL-C. Colesevelam as a monotherapy or add-on therapy for the treatment of type 2 diabetes mellitus can reduce A1C and LDL-C levels. Further, type 2 diabetes mellitus patients aged 65 years and older, colesevelam treatment as an add-on therapy results in similar A1C reductions. Colesevelam is safe and well-tolerated in older adults, with certain mild to moderate gastrointestinal side effects including constipation and dyspepsia. An advantage of prescribing colesevelam to older diabetic patients is the low risk for hypoglycemic events.

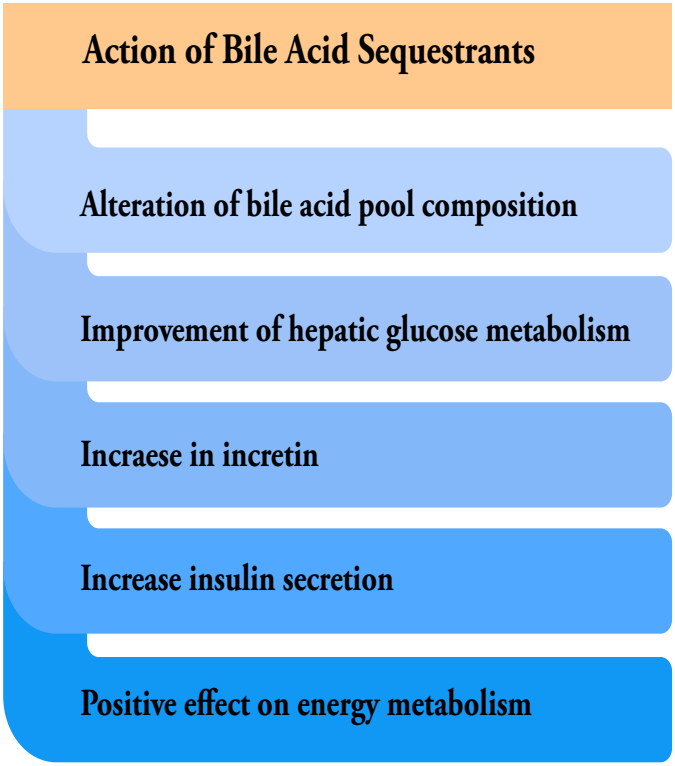

Figure 13: Action of Bile acid Sequestrants

Amylinomimetics

These agents mimic endogenous amylin effects by delaying gastric emptying, decreasing postprandial glucagon release, and modulating appetite.

Pramlintide is the example. This agent is a synthetic analogue of human amylin, a naturally occurring hormone made in pancreatic beta cells. It slows gastric emptying, suppresses postprandial glucagon secretion, and regulates food

intake because of centrally mediated appetite modulation.

Pramlintide is indicated for the treatment of type 1 or type 2 diabetes in combination with insulin. It is administered before mealtime in patients who have not achieved desired glucose control despite optimal insulin therapy. It helps to achieve lower blood glucose levels after meals, less fluctuation of blood glucose levels during the day, and improvement of long-term control of glucose levels (ie, HbA1C levels), compared with insulin alone. Additionally, less insulin use and a reduction in body weight are observed.

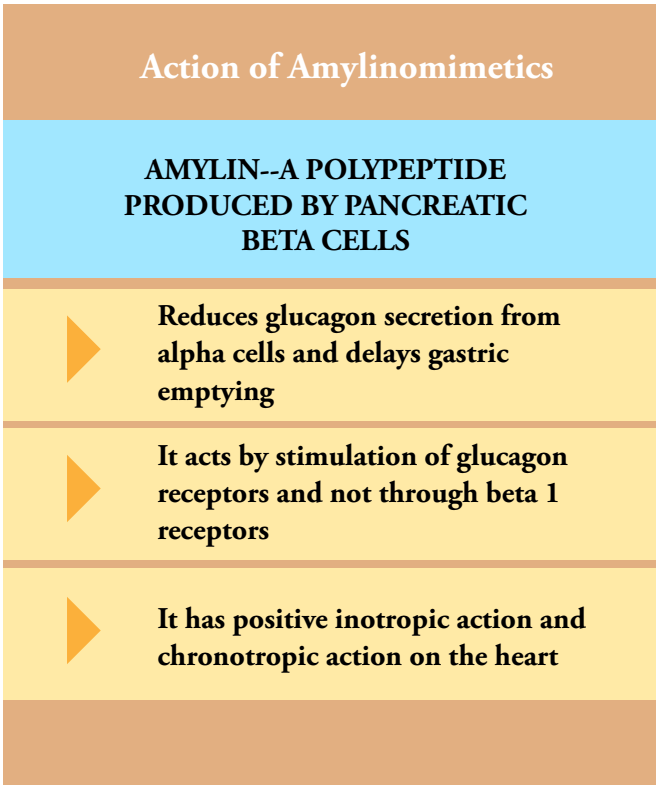

Figure 14: Action of Amylinomimetic

Pramlintide, an amylin analog, is an agent that delays gastric emptying, blunts pancreatic secretion of glucagon, and enhances satiety. It is a Food and Drug Administration (FDA)-approved therapy for use in adults with T1DM. Pramlintide induces weight loss and lowers insulin dose. Concurrent reduction of prandial insulin dosing is required to reduce the risk of severe hypoglycemia. Other medications that may lower blood sugar include bromocriptine, alpha-glucosidase inhibitors like voglibose and acarbose, and bile acid sequestrants like colesevelam. It may be noted that metformin sequesters bile acids in intestinal lumen and thus has a lipid-lowering effect, also the same mechanism may contribute to gas production and gastrointestinal disturbances. [12, Rank 4]

In patients with diabetes, dysregulation of multiple glucoregulatory hormones results in chronic hyperglycemia and an array of associated microvascular and macrovascular complications. Optimization of glycemic control, both overall (glycosylated hemoglobin [A1C]) and in the postprandial period, may reduce the risk of long-term vascular complications. However, despite significant recent therapeutic advances, most patients with diabetes are unable to attain and/or maintain normal or near-normal glycemia with insulin therapy alone. Pramlintide, an analog of amylin, is the first

in a new class of pharmaceutical agents and is indicated as an adjunct to mealtime insulin for the treatment of patients with type 1 and type 2 diabetes. By mimicking the actions of the naturally occurring hormone amylin, pramlintide complements insulin by regulating the appearance of glucose into the circulation after meals via three primary mechanisms of action: slowing gastric emptying, suppressing inappropriate post-meal glucagon secretion, and increasing satiety. In long-term clinical trials, adjunctive pramlintide treatment resulted in improved postprandial glucose control and significantly reduced A1C and body weight compared with insulin alone. The combination of insulin and pramlintide may provide a more physiologically balanced approach to managing diabetes.

Dopamine Agonists

Bromocriptine is a sympatholytic D2-dopamine agonist that has been approved for the treatment of type 2 diabetes. Based on animal and human studies, timed bromocriptine administration within 2 h of awakening is believed to augment low hypothalamic dopamine levels and inhibit excessive sympathetic tone within the central nervous system resulting in a reduction in postmeal plasma glucose levels due to enhanced suppression of hepatic glucose production. Bromocriptine has not been shown to augment insulin secretion or enhance insulin sensitivity in peripheral tissues.

In a 52 double-blind, placebo-controlled study in type 2 diabetic patients, bromocriptine reduced the composite cardiovascular end point by 40%.

> **“ Addition of bromocriptine to poorly controlled type 2 diabetic patients treated with diet alone, metformin, sulfonylureas, or thiazolidinediones produces a 0.5–0.7 decrement in HbA1c. Bromocriptine also reduces fasting and postmeal plasma free fatty acid (FFA) and triglyceride levels. ”**

Combinations of antidiabetic agents

Considering the importance of avoiding hypoglycemia and managing postprandial hyperglycemia in elderly patients, some combinations may provide these desirable outcomes better than commonly used metformin plus suphonyl urea in clinical practice. Current trials regarding drugs combination were not planned for the elderly patients except for a few studies including the elderly patients as a subgroup for further analysis. As the risk of hypoglycemia is higher in older adults, combination strategies with less hypoglycemia risk in middle-aged adults may be more appropriate for older adults. [15, Rank 3]

Metformin plus DPP4 inhibitors

When metformin monotherapy could not achieve glycemic target, DPP4 inhibitor was suggested as first add-on drug compared with sulphonyl ureas, thiazolidinediones, or insulin glargine in the elderly patients. Though not as effective as insulin glargine, combination of metformin with DPP4 inhibitors provided the favorable result of less hypoglycemia incidence. Compared with sulphonyl ureas, DPP4 inhibitor results in similar improvement of A1C, but less hypoglycemia incidence and no weight gain. This combination also showed better glycemic variability, decrease of glucagon production, better β-cell function, better insulin resistance, and better cost-effectiveness than a combination of metformin with sulphonyl ureas.

" Compared with TZD (thiazolidinediones), combination with DPP4 inhibitors revealed similar glycemic control and hypoglycemia risk, but less weight gain. Compared with metformin plus sulphonyl ureas, metformin plus thiazolidinediones was the more tolerable combination due to less hypoglycemia incidence with similar glycemic control and body weight gain. "

Metformin plus SGLT2 inhibitors

SGLT2 inhibitors are newly approved drugs without experience on long-term effect and safety. Randomized controlled studies demonstrated that combination with canaglifozin is at least not inferior to combination with glimepiride or sitagliptin in glycemic control, but with less hypoglycemia incidence than glimepiride and more body weight reduction than sitagliptin. This combination may provide favorable effects for elderly groups, but at the cost of more genitourinary tract infection. This risk should be balanced with other benefits during clinical practice.

Metformin plus acarbose

Effective on reduction of postprandial glucose excursion with low hypoglycemia risk makes Alpha-glucosidase inhibitors an attractive second-line therapy in elderly patients, at least theoretically. However, there was only one study with a small sample size comparing acarbose and glibenclamide as second-line combination therapy. Though not significant, Alpha-glucosidase inhibitors seemed less effective than sulphonyl ureas in glycemic control but had a favorable effect on body weight.

Triple combinations

Studies on triple combinations were limited. Most of the dual combinations in

clinical practice are metformin plus sulphonyl ureas. Some randomized controlled trials enrolled patients in poor control with metformin plus sulphonyl ureas and compared the effect of the third drug. Combination with canaglifozin 300 mg/day was superior to sitagliptin in glycemic control and body weight reduction without increased incidence of hypoglycemia. Acarbose had similar effects as repaglinide but was less effective than pioglitazone added on, despite favorable effect on body weight control.

Metformin and pioglitazone plus DPP4 inhibitors

If metformin and pioglitazone combinations were used as the first two orally administered drugs DPP4 inhibitors and sulphonyl ureas decreased A1C to a similar degree. DPP4 inhibitors had a neutral effect on body weight compared with body weight gain in sulphonyl ureas group. This combination was more tolerable than combination with sulphonyl ureas, such that no patients withdrew from the study due to hypoglycemia as compared with eleven patients in the sulphonyl ureas arm. This combination also demonstrated better protection of β-cell secretion.

Metformin and acarbose plus DPP4 inhibitors or mitiglinide

Despite the theoretical concern of the mismatch between peak glucose absorption and peak prandial insulin secretion in combination of acarbose with mitiglinides, a prospective randomized study revealed that daily blood glucose fluctuations were significantly improved without increase in incidence of hypoglycemia. For elderly patients poorly controlled with metformin monotherapy, a combination of AGIs plus DPP4 inhibitors or AGIs plus mitiglinide may be an attractive add-on choice. [16, Rank 5]

Glucose Monitoring

Self-monitoring of blood glucose and HbA1C are integral components of the standards of care in diabetes. They are designed to assess the effectiveness of a treatment plan and provide guidance in selecting appropriate medications and dosage/s. Self-monitoring of blood glucose allows patients to assess their own response to medication, minimize the risk of hypoglycemia, and determine whether they are achieving glycemic control. Optimal glycemic control is achieved when FPG is 70–130mg/dL, 2h post prandial <180 mg/dL, and bedtime glucose is 90–150 mg/dL. However, testing six to eight times daily may burden patients and may result in non-compliance. Therefore, it is recommended to ensure that patients are properly instructed and are given regular evaluation and follow-up.

Self-monitoring of blood glucose is

essential in patients with diabetes who are on intense insulin regimen (three to four injections of basal and prandial or insulin pump). It monitors and prevents hyperglycemia and possible side effect of hypoglycemia. Blood glucose level is usually checked prior to meals, prior to exercise, prior to driving, and at bedtime. Evidence is insufficient to prescribe Self-monitoring of blood glucose for patients not receiving an intensive insulin regimen.

According to the current guideline, HbA1C level should be assessed regularly in all patients with diabetes. The frequency of HbA1C testing is flexible and depends primarily on the response of patients to therapy and the physician's judgment. HbA1C testing is performed at least every 6 months for patients who are meeting treatment goals; for patients, who are far from their glycemic goals, HbA1C testing may be performed more frequently. [7, Rank 3]

Future Perspectives

Unfortunately, all anti-diabetic agents have adverse effects, and are expensive. Therefore, the investigation of novel antidiabetic regimens, with less adverse effects and cheaper, is a major challenge for researchers.

Polyphenols

Natural products containing high polyphenol levels as blackberries, red grapes, apricots, eggplant, coffee, cocoa and green tea can regulate glucose metabolism through different paths, such as restoring beta-cell integrity, enhancing insulin releasing activity, and increasing cellular glucose uptake, which can improve insulin resistance.

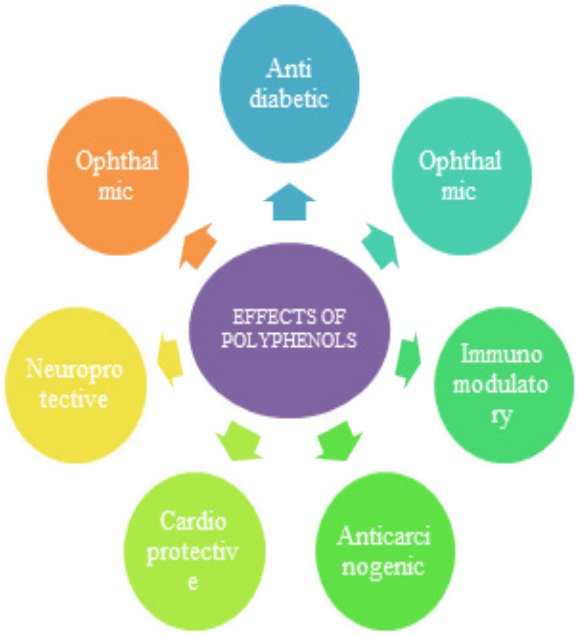

Figure 13: Action of Bile acid Sequestrants

Smart Insulin Patch

A new smart insulin patch has been created. It is a thin square covered with more than 100 tiny needles. The patch made of biocompatible materials works fast and it's easy to use. The patch consists of small painless needles that are packed together with insulin and glucose-sensitive enzymes in microscopic storage units. The patch releases these enzymes when blood glucose increases. In a mouse model, patch

administration showed reduced glucose levels up to 9 h. It is suggested that the patch could have a longer effect in diabetic humans since humans are more sensitive to insulin than mice.

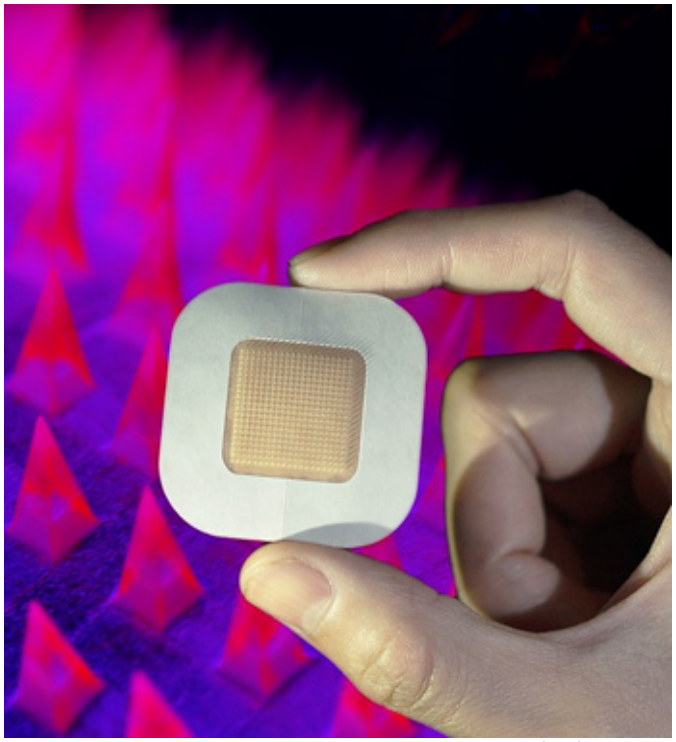

Image source: Wikimedia Commons

Figure 16: Smart Insulin Patch

Dual-acting peptide

Glucagon-like peptide 1 (GLP1) and Gastric inhibitory polypeptide (GIP) is the two main incretin hormones that are released from the intestine in response to food intake. Both hormones stimulate glucose-dependent insulin secretion. Evidence from animal studies suggests that anti-obesity efficacy of Glucagon-like peptide 1 can be enhanced by co-administration with the incretin hormone GIP. An acylated version of Glucagon-like peptide 1 and Gastric inhibitory polypeptide dual agonist, reduced weight (-18.8% vs -8.8%, $P < 0.001$), food intake ($P < 0.05$), fat mass ($P < 0.001$) and blood glucose ($P < 0.05$), compared to liraglutide. Also showed increases in plasma insulin and C-peptide more pronounced that liraglutide ($P < 0.001$ for both). No differences in improved glycaemic control between these co-agonists and liraglutide were found. In T2DM patients they found a dose-dependent reductions of HbA1c, being -0.53% in patients treated with 4 mg of the dual agonist, and -1.11% in those treated with 30 mg, compared with placebo (-0.16%). The pharmacokinetics and pharmacodynamics results of co-activation of Glucagon-like peptide 1 and Gastric inhibitory polypeptide receptors are considered as a promising new strategy for the treatment of obese T2DM patients, to prolong the activity of Glucagon-like peptide 1 and Gastric inhibitory polypeptide dual agonists, and for the future development of a possible once-weekly Glucagon-like peptide 1 and Gastric inhibitory polypeptide dual agonists drug candidate for the treatment of Type 2 DM.

GLP1 (Glucagon-like peptide 1) and Glucagon receptor dual agonism

Glucagon and GLP1 have distinct receptors that are also structurally related.

Glucagon stimulates gluconeogenesis and glycogenolysis in the liver, raising blood glucose levels; while GLP1 reduce blood glucose levels by increasing insulin synthesis and secretion in the pancreas. Administration of oxyntomodulin, a GLP1 receptor/-glucagon receptor dual agonist peptide, to rodents and humans, resulted in a improvement of glucose metabolism by decreasing food intake and body weight, and increasing energy expenditure, more pronounced than those reported by GLP1. Moreover, weekly administration of PEGylated peptides reduced adiposity and improved glucose tolerance in diet-induced obese mice, and sustained GLP1/glucagon dual agonism reverses obesity in diet-induce obese mice. These co-agonist compounds also normalized glucagon, glucose and lipid metabolism and reduced liver steatosis, and is a novel therapeutic approach to the treatment of obesity in patients with Type 2 DM.

GLP1 receptor agonist and Glucagon receptor antagonism activity

GLP1/ Glucagon hybrid peptides, a dual acting peptide that bind both receptors, for diabetes (DAPD) have been reported previously and more recently have been identified in vitro. Administration of PEGylated DAPD in mice, showed a decrease in blood glucose by increasing insulin secretion GLP1-induced, and a rise in fasting glucagon levels following a glucagon challenge. Moreover, unlike RA-GLP1, does not inhibit gastrointestinal motility and has not adverse events at this level.

Basal insulin analogs with glucagon-like peptide-1 mimetics

The combination of GLP1 mimetics with basal insulin reduced the risk of hypoglycaemia and weight gain induced for intensive insulin regimens in Type 2 DM patients. Preliminary evidence suggests that the addition of basal insulin to a GLP1 mimetic with or without oral therapy provide improvements in basal and postprandial glucose control, with less weight gain, reduced risk of hypoglycaemia and increased satisfaction. Data from the DUAL I extension (insulin-naïve patients not controlled with oral hypoglycaemic agents) and DUAL II (patients not controlled on basal insulin plus oral hypoglycaemic agents) randomized trials, the novel fixed combination of insulin degludec and liraglutide (IDegLira), effectively lowered HbA1c across a range of measures, implying suitability for patients with either early or advanced Type 2 DM. LixiLan is a new once-daily single injection fixed-ratio combination of lixisenatide, and insulin glargine. Results from the Lixilan-L trial, showed that LixiLan successfully met the primary study endpoint of demonstrating a statistically superi-

or reduction in HbA1c compared with insulin glargine.

G protein-coupled receptor 119

G protein-coupled receptor 119 (GPR119) agonists is a G protein-coupled receptor that is expressed predominantly in the pancreas and gastrointestinal tract in rodents and humans, as well as in the brain in rodents. Activation of the receptor showed a reduction in food intake and body weight gain in rats. GPR119 has also been shown to regulate incretin and insulin secretion.

It is worth pointing out the potential advantages that could be obtained by the co-administration of a GPR119 agonist and a iDPP4.

Oral RA-GLP1

Currently, RA-GLP1s (Receptor Agonists Glucagon-like peptide 1) are available only as injectables, either once daily or once weekly.

> **" Semaglutide is a long-acting Receptor Agonists Glucagon-like peptide 1 (RA-GLP1) that is also being developed as a once-weekly injectable. An oral semaglutide version leading to higher solubility and protection from enzymatic degradation is also being developed. "**

The phase 2 study enrolled 632 adults with T2DM of 6 to 7 years duration, managed with lifestyle with or without metformin, and HbA1c 7.0% to 9.5% (mean, 7.9%). They were randomized to oral semaglutide in doses of 2.5, 5, 10, 20 or 40 mg once daily, or to placebo, or to open-label injected once-weekly 1.0-mg semaglutide. Patients started at 2.5 or 5 mg once daily and the higher-dose groups were titrated up at 4-wk intervals. The primary endpoint was change in HbA1c from baseline to week 26.

At 26 wk, mean HbA1c decreased dose-dependently with oral semaglutide, with drops ranging from 0.7% with 2.5 mg to 1.9% with 40 mg. Subcutaneous once-weekly semaglutide also produced a 1.9% drop in HbA1c, while the placebo group experienced a decrease of only 0.3% ($P = 0.07$ for 2.5 mg vs placebo, $P < 0.0001$ for other doses). For all the groups taking 5-mg oral semaglutide or higher doses, more than 80% of the patients achieved HbA1c values less than 7%, and the groups treated with 10-mg dose or more achieved mean HbA1c less than 6.5%. Fasting plasma glucose also dropped significantly, from a baseline of 170 mg/dL, with reductions ranging from 17 mg/dL with 2.5 mg to 51 mg/dL for the other oral doses (P=

0.08 for 2.5 mg, P < 0.0001 for other doses) and a reduction of 56 mg/dL with 1.0-mg subcutaneous semaglutide vs 1 mg/dL with placebo.

The proportion of patients achieving 5% or more weight loss was 21% to 71% in the oral group and 66% in subcutaneous group, compared with 13% in the placebo group.

None of the adverse events were considered serious and all were reported as mild to moderate in severity. Increases in lipase levels were greater in the oral and subcutaneous semaglutide groups, compared with placebo. Based on these data, oral semaglutide is now being studied in a large phase 3 trial.

Oral insulin

Oral administration of insulin is a novel treatment to improve glycaemic control in patients with T2DM. Oral insulin has a more physiological action than parenteral insulin. Due to its first pass through the liver, it reduces glycogenolysis, hepatic glucose production, and the risk of hypoglycaemia, compared with parenteral insulin.

Dual inhibition of SGLT1 and SGLT2

Sotagliflozin is a dual inhibitor of SGLT1 and SGLT2 with approximately 20-fold selectivity for SGLT2 over SGLT1. Animal pharmacology studies showed that sotagliflozin produced increased urinary glucose excretion, delivery of glucose to the caecum, increased postprandial GLP1 and peptide YY release, that were related with significant reductions in postprandial glucose. Sotagliflozin was evaluated in patients with T2DM not controlled with metformin. Sotagliflozin reduced fasting plasma glucose and HbA1c with a modest urinary glucose excretion, compared with selective iSGLT2. The high glycaemic efficacy observed with only modest urinary glucose excretion suggested that clinically relevant gastrointestinal SGLT1 inhibition was present. Phase 1 and phase 2 studies have identified special opportunities for synergy with iDPP-4 for treatment of patients with T2DM and renal impairment.

Other treatments

Technosphere insulin, a new inhaled insulin represent an alternative to bolus insulin injections, but can be used concomitantly with basal insulin injections. Its hypoglycaemic effect is less than the rapid-acting insulin, but has less hypoglycaemia. Major adverse effects are respiratory, with cough being the most prominent, and there is a small decrease in the forced expiratory volume in 1 s (FEV1) with technosphere insulin, consistent, no progressive, and reversible; so that patients must receive

pulmonary function test periodically throughout therapy.

New chitosan formulations of xanthine derivatives (CS-6, CS-7) have been synthesized as antidiabetic and antioxidant treatments. Formulations of chitosan 6 (CS-6) have shown to reduce blood glucose levels by 59.3%, with a recorded 4.53% HbA1c level. These effects were more intense than the induced by pioglitazone (114.5 mg/dL vs 148.5 mg/dL), when used as standard antidiabetic medication. These results have shown the potential application of chitosan formulations of Xanthine 6 derivates (CS-6) in the treatment of diabetes mellitus.

Recent studies have shown the dynamic role of zinc, an insulin mimetic, as a "cellular second messenger" in glucose homeostasis and in the control of insulin signaling. Synthesis, secretion and insulin action are dependent on zinc and transporters. This suggests that zinc plays a role, previously not identified, where changes in the state of zinc over time can affect the activity of insulin. This is a novel area of investigation, and introduces a new class of useful drugs for diabetes pharmacotherapy.

Imeglimin is the first of the family of agents called glimins and, more specifically, is a tetrahydrotriazene compound. Laboratory studies have shown that acts on impaired glucose uptake by muscle tissue, excessive hepatic gluconeogenesis, and increased apoptosis of beta cells. This reduces HbA1c and fasting glucose similar to sitagliptin and metformin, with a low incidence of side effects, especially hypoglycaemia. Imeglimin seems to be a promising antidiabetic agent as monotherapy in the treatment of T2DM.

Recent studies reported a possible role of the G protein coupled receptor 40 (GPR40), also known as FFAR 1, in the regulation of beta-cell function. It was reported that chronic treatment of male zucker diabetic fatty (ZDF) rats (insulin resistant model with elevated blood glucose and FFAs levels) with CNX-011-67 (GPR40 agonist) increased insulin secretion, decreased blood glucose and reduced beta-cell apoptosis without affecting body weight. CNX-011-67 could have the potential to provide good and durable glycaemic control in T2DM patients. Another study provided evidence that activation of GPR40 with CNX-011-67 stimulates glucose metabolism, improve glucose responsiveness and enhances insulin secretion, with the hope that pharmacological activation of GPR40 will prove beneficial for the treatment of T2DM. TAK-875, a novel highly selective, orally bioavailable GPR40 agonist, significantly improved glycaemic control in patients with T2DM with a minimum risk of hypoglycaemia. The outcomes

show that activation of FFAR1 is a viable therapeutic target for the treatment of T2DM. According to current data it can be appreciated that beta-cell failure could be delayed or prevented by attaining and maintaining good glycaemic control.

Finally, in vivo studies, administration of hot water extracts of Salacia chinensis to diet-fed KK-Ay mice, resulted in a significant reduction in the basal and postprandial blood glucose and HbA1c levels; with an improvement of glucose tolerance. The active components, salacinol, kotalanol, and neokotalanol inhibited human α-glucosidases as potently as they inhibited rat small intestinal α-glucosidase. [15, Rank 3]

Potential Drug Targets

Many potential drug targets are currently under investigation.

A phase 2 trial revealed that the glucose-lowering effects of TAK-875 and the sulfonylurea glimepiride are comparable, but less hypoglycaemic events occurred in the group treated with TAK-875. However, weight gain was similar in both patient groups treated either with glimepiride or with TAK-875. The long-term effects of this novel drug-like protection or maintenance of beta-cell mass or the prevention of cardiovascular complications remain to be seen.

Another potential drug target within the beta-cell, but not exclusively there, is the activation of the glucokinase. In beta-cells, glucokinase acts as a glucose sensor and by phosphorylation of glucose triggers glucose oxidation, insulin biosynthesis and insulin secretion. In hepatocytes, this enzyme enhances glycolysis, glycogen synthesis and lipogenesis. Thus, activators of glucokinase effectively lower blood glucose levels by increased beta-cell insulin release and decreased hepatic glucose output. Heterozygous inactivating mutations of glucokinase cause maturity-onset diabetes of the young characterized by mild fasting hyperglycaemia; homozygous inactivating mutations result in permanent neonatal diabetes mellitus, demonstrating the importance of this enzyme for glucose homeostasis. Furthermore, after 3–4 months of treatment, the drug failed. Two structurally distinct glu-

“ TAK-875 (Fasiglifam) an agonist of the G-protein coupled receptor/free fatty acid receptor 1 (GPR40/FFAR1) highly expressed on beta-cells, is one example for a novel anti-diabetic drug. In isolated rat and human islets, TAK-875, by binding to its receptor, increased the intracellular calcium concentration and activated PKC, thereby potentiating glucose-stimulated insulin ”

cokinase activators induced hepatic steatosis in normoglycaemic and diabetic rodents. Hence, the long-term activation of glucokinase might not be beneficial at all.

Glucagon is another quite intriguing target for the therapy of diabetes. This peptide hormone is secreted from the pancreatic α-cells in response to mixed meal nutrients, amino acids and hypoglycaemia. Glucagon secretion and biosynthesis is inhibited by insulin and probably other factors, secreted by the neighbouring beta-cells. Glucagon binds to its Gs-protein coupled receptor on hepatocytes, thus stimulating gluconeogenesis and enhancing glucose output. Hence, glucagon, elevating fasting glucose levels, can be considered as a functional antagonist of insulin, decreasing postprandial glucose levels.

The relevance for targeting glucagon receptors or α-cells to interfere with the pathogenesis of diabetes has long been neglected. Glucagon levels are enhanced in poorly controlled type 1 and type 2 diabetes, and some type 2 diabetic patients with at least moderately controlled glucose levels show fasting hyperglucagonaemia. Dysfunction of the α-cells might contribute to the pathogenesis of type 2 diabetes: in diabetic patients, α-cell response to hyperglycaemia is blunted and glucagon secretion is enhanced by physiological stimuli to a greater extent than in non-diabetics. In addition, the α-cell itself might become insulin resistant, failing to reduce glucagon biosynthesis and secretion in response to insulin. Hence, blocking glucagon action is a suitable target for treating type 2 diabetes mellitus. Glucagon-receptor knockout mice and treatment of several animal models with antibodies against glucagon or antisense oligonucleotides against the glucagon receptor support this notion. However, α-cell hyperplasia with elevated glucagon and GLP-1 levels, and hepatic steatosis has been observed in animal models. It should be noted that already drugs exist that interfere with glucagon action: GLP-1 analogues and DPP 4 inhibitors reduce α-cell glucagon secretion; metformin seems to inhibit hepatic glucagon action by indirectly inhibiting the adenylate cyclase of the Gs-coupled glucagon receptor.

Guided by the observation that an excess of glucocorticoids (Cushing's syndrome) shows similarities to the metabolic syndrome with obesity, insulin resistance and diabetes, decreasing local concentrations of hydrocortisone (cortisol) has become another alternative for the treatment of type 2 diabetes. Cortisol, produced and secreted from the adrenal glands, induces hyperglycaemia by promoting hepatic gluconeogenesis and glycogenolysis. In the presence of NADPH, 11β-hydroxysteroid dehydrogenase 1 (11β-HSD 1)

converts the inactive cortisone to the active cortisol. This enzyme is mainly expressed in liver and the adipose tissue. The 11β-HSD 2 is mainly expressed in tissues that also express the mineralocorticoid receptor such as the kidney and oxidizes cortisol to cortisone, thus allowing aldosterone to bind to its receptor. Mice deficient in 11β-HSD 1 or treated with specific 11β-HSD 1 inhibitors show improved glucose tolerance, reduced insulin resistance and decreases in body weight. The effects seem to be mainly due to the inhibition of the adipose tissue enzyme. In type 2 diabetic patients treated for 12 weeks with INCB13739 in addition to metformin therapy, reduced HbA1c levels (by 0.6%) and fasting glucose levels were observed. Other 11β-HSD 1 inhibitors tested in diabetic patients had negligible effects on glucose metabolism.

" Taking into account the inflammatory nature of diabetes, immune-modulating therapies may be another option for the treatment of type 2 diabetes mellitus. The pro-inflammatory cytokine IL-1β seems to initiate the migration of macrophages to the inflamed adipose tissue and islets. "

Furthermore, IL-1β is secreted from the beta-cells themselves in hyperglycaemia, inhibits insulin gene transcription and induces beta-cell apoptosis. Hence, attenuating this cytokine's effect represents a promising target. In a double-blind trial, type 2 diabetic patients were randomized to placebo or to treatment with the recombinant human IL-1-receptor antagonist anakinra administered once daily s.c. for 13 weeks. Treatment with anakinra lowered HbA1c by 0.46% and reduced the markers of systemic inflammation. In a 39 week follow-up study, the anti-inflammatory effect of anakinra was still present, whereas the improvement in HbA1c levels was no longer detectable. Other IL-1β neutralizing antibodies are currently investigated in clinical trials. TNF-α is secreted from the adipose tissue in the pre-diabetic state and is elevated in obesity, insulin resistance and type 2. A recent study demonstrated that treatment of obese, insulin-resistant patients with the recombinant TNF-α receptor 2 etanercept for 6 months improved fasting glucose levels. These findings suggest that targeting the chronic, low-grade inflammation might provide a useful drug target. In fact, the glucose-lowering effect of a well-known anti-inflammatory drug was described already more than 100 years ago. [18, Rank 2]

If the HbA1C level rises to 7.5%

while on medication or if the initial HbA1C is ≥9%, combination therapy with two oral agents, or with insulin, may be considered. Though these medications may be used in all patients irrespective of their body weight, some medications like liraglutide may have distinct advantages in obese patients in comparison to lean diabetics. [4, Rank 2]

Three classes of novel antihyperglycemic agents, sodium-glucose cotransporter-2 (SGLT2) inhibitors, glucagon-like peptide-1 receptor agonists (GLP-1RA), and dipeptidyl peptidase-4 (DPP4) inhibitors have demonstrated varied cardiorenal outcomes in recent cardiovascular outcomes trials.

Conclusion

While lifestyle modifications and metformin are the cornerstone of the initial management of Type 2 Diabetes Mellitus, there is an increasing array of second and third-line pharmacological agents for this condition. At present there are different families of oral and injectable drugs, available for the treatment of T Type 2 Diabetes Mellitus. These include sulfonylureas, meglitinides, insulin, thiazolidinediones and alpha-glucosidase inhibitors, and recently with the addition of RA-GLP1 receptor agonists, iDPP4 and iSGLT2. Moreover, insulin analogues that better simulate endogenous insulin secretion have been developed. Metformin remains the first choice of treatment for most patients. Other alternative or second-line treatment options should be individualized taking into consideration patient characteristics as degree of hyperglycaemia, presence of co-morbidities, and patient preference and ability to access treatments; and properties of the treatment such effectiveness and durability of lowering blood glucose, risk of hypoglycaemia, effectiveness in reducing diabetes complications, effect on body weight, side effects and contraindications. Although it does not appear that in the near future cure diabetes, novel safety and effective agents that will improve the quality of life of Type 2 Diabetes Mellitus patients, are developing. [7, Rank 3]

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