Medications for Hyperglycemia in Type 2 Diabetes and Review of Insulin Degludec and Dapagliflozin

Dr. Sheikh Salahuddin Ahmed[1], Dr. Tarafdar Runa Laila[2]

[1.] *Professor and Head, Department of Internal Medicine, Bangladesh Institute of Health Science, Dhaka,*
[2.] *Assistant Professor, Department of Obs & Gyne, Bangabandhu Sheikh Mujib Medical University, Dhaka,*

ABSTRACT: *Patients with type 2 diabetes mellitus (T2DM) are usually treated with pharmacologic agents in combination with lifestyle modifications. Recently 2 drugs one being the injectable ultra-long acting analog insulin, degludec and the other being oral sodium glucose cotransporter 2 (SGLT2) inhibitor, dapagliflozin have been introduced to supplement the previous antidiabetic agents. The objective of this review article is to discuss the current pharmacological agents available, their successes, demerits and limitations in the treatment of patients with T2DM. This article also reviews currently available knowledge about degludec and dapagliflozin. Informations have been gathered from related clinical studies, research works, articles and abstracts published in various journals. It is generally agreed that metformin, if not contraindicated and if tolerated, is the preferred and most cost-effective first line agent for the treatment of T2DM. Insulin analogs are also becoming mainstream therapy for T2DM. Insulin degludec administered once daily is found to be significantly less variable and more stable in maintaining euglycemia as compared to insulin glargine and has flexibility in dosing time. It also causes lower incidence of hypoglycemia in both type 1 and type 2 diabetic patients. SGLT2 inhibitors are the most advanced new oral antidiabetic agents that lower glycosylated hemoglobin by increasing glycosuria and lead to a moderate weight loss. Dapagliflozin represents a novel approach to the management of T2DM.*

KEYWORDS: *Antidiabetic, Diabetes, Dapagliflozin, Hyperglycemia, Insulin Degludec*

I.   INTRODUCTION

Diabetes mellitus continues to be a global public health problem and a major cause of morbidity. The incidences of both type 1 and type 2 diabetes are rising. The global pandemic principally involves T2DM which is associated with greater longevity, obesity, unsatisfactory diet, sedentary lifestyle and increasing urbanization [1]. T2DM accounts for approximately 90%-95% of all cases of the disease [2]; consequently, efforts to improve outcomes have focused on this population. Diabetes has substantial adverse effects on health status and life span, and carries high societal costs. T2DM remains a leading cause of cardiovascular (CV) disorders, blindness, end-stage renal failure, non-traumatic lower limb amputations, and hospitalizations. It is also associated with increased risk of cancer, cognitive decline, chronic liver disease, and other disabling or deadly conditions [3]. Patients with T2DM are usually treated with pharmacologic agents in combination with lifestyle modification. The large number of new classes of agents developed after 1995 reflects the increase in our understanding of the multiple targets for improving hyperglycemia and has led to treatment strategies that enable many patients with T2DM to achieve target glycosylated hemoglobin (HbA1c) levels (≤7.0%) [4]. The availability of number of treatment options by the practitioners for diabetes therapy also provides a chance for successful management in a larger number of patients. But at the same time widening array of pharmacological agents now available has heightened uncertainty regarding the most appropriate means of treating this widespread disease. Pharmacologic treatment of patients with T2DM is limited not only by the effectiveness of the agents but also by their adverse effects, cost, patient's preferences, needs, and values. Although numerous reviews on the management of T2DM have been published in the past and recent years, practitioners are often left without a clear pathway of therapy to follow. This review article discusses the current pharmacological agents in use, their successes, merits, demerits and limitations in the treatment of patients with T2DM. This article also reviews currently available knowledge about the novel insulin analogue, degludec and the SGLT2 inhibitor, dapagliflozin.

II.   OVERVIEW OF PATHOPHYSIOLOGY OF TYPE 2 DIABETES

T2DM is a disease that is heterogeneous in both pathogenesis and in clinical manifestation—a point to be considered when determining the optimal therapeutic strategy for individual patients. The interaction between several genetic and environmental factors results in this progressive disorder with variable degrees of insulin resistance and insulin deficiency resulting from pancreatic β-cell dysfunction [5,6].

Elevated levels of fatty acids and post-inflammatory cytokines secondary to overweight and obesity are attributable to cause insulin resistance. Insulin resistance in muscle and liver is generally thought to be the first step in the development of T2DM, but the disease does not occur in the absence of progressive β-cell failure. In liver, the insulin resistance is manifested by an overproduction of glucose during the basal state. So in the fasting state, hyperglycemia is directly related to increased hepatic glucose production. In the postprandial state, hyperglycemia is related to defective insulin stimulation of glucose disposal in target tissues, mainly skeletal muscle with impaired glucose uptake following ingestion of a carbohydrate meal [7]. The decline in β-cell function seems to involve chronic hyperglycemia (glucotoxicity), chronic exposure to free fatty acids (lipotoxicity), oxidative stress, inflammation, and amyloid formation [8-11].

In addition to the liver, muscle and β-cell, the α-cell of the pancreas (increased glucagon secretion in the presence of hyperglycemia), gastrointestinal tract (incretin deficiency), fat cell (accelerated lipolysis), kidney (increased glucose reabsorption), and brain (insulin resistance) all play important roles in the development of T2DM [7]. Collectively, these eight players comprise the ominous octet and dictate that multiple drugs used in combination will be required to correct the multiple pathophysiological defects, and that therapy must be started early to prevent/slow the progressive β-cell failure. Amylin is a natural hormone produced by the β-cell of the pancreas and is co-secreted with insulin in response to a glucose load. It inhibits glucagon production, slows gastric emptying, and also stimulates satiety. In T2DM, there is impairment of amylin secretion by the pancreatic β-cells. Abnormalities in the incretin system (Glucagon like peptide-1 or GLP-1) have also been recognized to contribute in the pathogenesis of T2DM [12]. GLP-1 is a naturally occurring peptide produced by the l-cells of the small intestine. In addition to stimulating glucose dependant insulin secretion, GLP-1 suppresses glucagon and slows gastric emptying, and also acts on the hypothalamus to induce satiety.

III. ANTIDIABETIC DRUGS

Treatment options have greatly expanded in the past two decades. Available agents reduce glucose levels, often through a variety of mechanisms. Currently, 12 unique classes of drugs are available for the treatment of patients with T2DM in most countries, and are approved by the Food and Drug Administration (FDA) for their use in United States (US). The glycemic control in T2DM is achieved with some agents that predominantly lower the fasting plasma glucose level (metformin, sulfonylureas and basal insulins); with others that primarily lower postprandial plasma glucose excursions (meglitinides, α-glucosidase inhibitors [AGIs], pramlintide, exenatide and prandial insulins); and with still others that do both (thiazolidinediones [TZDs], dipeptidyl peptidase-4 [DPP-4] inhibitors, liraglutide and premixed insulins) [4]. The glucose-lowering effectiveness of noninsulin pharmacological agents is said to be high for metformin, sulfonylureas (SUs), TZDs, and GLP-1 analogs, and generally lower for meglitinides, alpha-glucosidase inhibitors (AGIs), DPP-4 inhibitors, colesevelam, and Bromocriptine [13-15].

1.1 Oral agents

Oral agents that improve insulin secretion by the pancreatic beta cells are known as insulin secretagogs and are sulfonylureas, meglitinides and more recently incretin mimetics [16-18]. Secretagogs should be given to patients with reasonable residue of functioning beta cell and is useless in the presence of total beta cell exhaustion. Insulin sensitizers are metformin, TZDs and recently D2 dopamine receptor agonists [1]. Metformin predominately acts by reducing hepatic glucose output and thereby lowering fasting hyperglycemia, whereas TZDs mainly by improving insulin sensitivity in the skeletal muscles [19,20]. The AGIs delay carbohydrate absorption in the gut by selectively inhibiting intestinal α-glucosidase [21]. The DPP-4 inhibitors inhibit degradation of native GLP-1 and thus enhance incretin effect i.e. prolongs half-life of GLP-1. GLP-1 analogs have been thought to be potential for improving beta cell mass and function [22,23].

1.1.1. BIGUANIDE: The only drug used now in this class is metformin. It remains the most widely used first-line drug for the treatment of type 2 diabetes. Metformin seldom causes hypoglycemia as monotherapy; it is generally well tolerated, not associated with weight gain and has been used safely. The most common adverse effects are gastrointestinal like abdominal discomfort, cramps, anorexia, nausea and diarrhea. It is sometimes associated with vitamin B12 deficiency and some people may need to take B12 supplements. Metformin is cleared by the kidneys and in chronic kidney disease (CKD), toxic levels of metformin can accumulate leading to lactic acidosis. Renal dysfunction is considered a contraindication to metformin use due to increase risk of lactic acidosis, an extremely rare but potentially fatal complication. Current US prescribing guidelines warn against the use of metformin in patients with a serum creatinine ≥133 mmol/L (≥1.5 mg/dL) in men or 124 mmol/L (≥1.4 mg/dL) in women [3]. However, recent studies have suggested that metformin is safe unless the estimated glomerular filtration rate (GFR) falls to <30 ml/min with dose reduction advised at 45 mL/min [24-26]. In united Kingdom (UK) treatment with metformin is withdrawn when creatinine is higher than 150 μmol/L

(1.7 mg/dL) [1]. Other contraindications of metformin are acidosis, dehydration and hypoxia[3]. Metformin should not be used if alanine aminotransferase (ALT) is 2.5-3 times normal upper limits [27]. Metformin, previously contraindicated in heart failure, can now be used if the ventricular dysfunction is not severe, if patient's CV status is stable, and if renal function is normal [28].

1.1.2. SULFONYLUREAS (SUs): The oldest oral agent class is the sulfonylurea insulin secretagogues. Examples of 2nd generation SUs are glibenclamide (in US known as glyburide), glipizide, gliclazide and glimepiride. SUs are valuable in the treatment of non-obese patients with T2DM who fail to respond to lifestyle modification alone. The major adverse side effect is hypoglycemia, which can be prolonged and life threatening, and are relatively more frequent in the elderly. The SUs are contraindicated in moderate to severe liver dysfunction due to increased risk of hypoglycemia; and should not be used during acute CV events. Glibenclamide which has a prolonged duration of action should not be used in renal failure [1,3]. In addition, studies have demonstrated a secondary failure rate by SUs that may exceed other drugs, ascribed to an exacerbation of islet dysfunction [29]. The problems of unwanted hypoglycemia, weight gain, and beta cell failure are limiting the use of SUs after availability of modern drugs. The glycemic benefits of SUs are nearly fully realized at half-maximal doses, and higher doses should generally be avoided [25].

1.1.3. MEGLITINIDES: The meglitinides (repaglinide and nateglinide) have short duration of action, lowers postprandial glucose level and needs frequent dosing. As such these drugs are indicated for postprandial hyperglycemia. Of the two glinides, nateglinide is somewhat less effective in lowering HbA_{1c} than repaglinide when used as monotherapy or in combination therapy[13]. These drugs are associated with hypoglycemia and weight gain. Hypoglycemia is less as compared to SUs [30]. Meglitinides can be used in liver dysfunction [3]. They do not undergo significant renal clearance but caution is imperative at more severe degrees of renal dysfunction [3].

1.1.4. THIAZOLIDINEDIONES (TZDs): The drugs in this class include pioglitazone and rosiglitazone. TZDs are most likely to be effective in patients with pronounced insulin resistance (e.g. in abdominal obesity). Other advantages are: no risk of hypoglycemia, increase in high density lipoprotein (HDL) cholesterol and decrease in triglycerides. Pioglitazone is not eliminated renally, and therefore there are no restrictions for use in chronic kidney disease (CKD) [3]. There is preliminary evidence that patients with fatty liver may benefit from treatment with pioglitazone[3]. The most common adverse effects with TZDs are weight gain and fluid retention with peripheral edema. TZDs must be avoided in patients with cardiac failure. TZDs should not be used if ALT is 2.5-3 times normal upper limits [3,27]. In addition both the drugs have increased risk of fracture and bone loss particularly in women [31], thus the appropriate use in patients with underlying bone disease (such as renal osteodystrophy) needs to be considered. TZDs increase peripheral (subcutaneous) adipose tissue mass with some reduction in visceral fat [25]. In July 2007 a study has shown a 40% increase risk of CV events and deaths among users of rosiglitazone [32]. Thereafter rosiglitazone prescription is highly restricted in US and the drug is withdrawn in Europe [3,33]. Pioglitazone has recently been associated with a possible increased risk of bladder cancer and has drawn attention [34]. In June 2011, France and Germany suspended use of pioglitazone. FDA & European Medicines Agency (EMA) are recommending that T2DM patients with current bladder cancer, a history of the disease, or uninvestigated macroscopic hematuria, should not be prescribed pioglitazone.

1.1.5. ALPHA-GLUCOSIDASE INHIBITORS (AGIs): Acarbose, miglitol and voglibose are the drugs in this group. The AGIs are effective in lowering postprandial hyperglycemia modestly without causing hypoglycemia but may have gastrointestinal side effects. There may be slight reduction in the body weight and serum triglycerides. They are less effective in lowering glycemia than metformin or the sulfonylureas when used as monotherapy. A high frequency of gastrointestinal side effects limits their use. In renal dysfunction use of AGIs needs consideration. They are only minimally absorbed, serum levels of the drug and its metabolites increase significantly with reduced kidney function. Although no adverse effects have been reported, its use in patients with a GFR<26 mL/min/ 1.73 m2 is not recommended [35].

1.1.6.. DPP-4 INHIBITORS: The DPP-4 inhibitors or gliptins are sitagliptin, vildagliptin, saxagliptin, linagliptin and alogliptin. The first DPP-4 inhibitor, sitagliptin, was approved by the FDA in October 2006 for use as monotherapy or in combination with other drugs. Another DPP-4 inhibitor, vildagliptin, was approved in Europe in February 2008 [25]. The DPP-4 inhibitors reduces postprandial glucose excursion. They do not cause hypoglycemia when used as monotherapy and are weight neutral drugs. A limiting side effect is nausea and vomiting, particularly early in the course of treatment. The potential for this class of compound to interfere with immune function is of concern and an increase in upper respiratory infections has been reported. Cases of urticaria, angioedema and exfoliative dermatitis have been observed [7].

In patients with mild hepatic disease, incretin-based drugs can be prescribed, except if there is a coexisting history of pancreatitis [3]. Among the DPP-4 inhibitors, sitagliptin, vildagliptin, and saxagliptin share prominent renal elimination. In the face of advanced CKD, dose reduction of sitagliptin, vildagliptin, and saxagliptin is necessary. The DPP-4 inhibitors are expansive and their long term safety profile remains unknown [23].

1.1.7. BILE ACID SEQUESTRANTS: In January, 2008, the FDA approved the bile acid sequestrant colesevelam as an adjunctive therapy to improve glycemic control in adults with T2DM. It binds to intestinal bile acids/cholesterols, and by unknown mechanism reduces hepatic glucose production and increases incretin levels to lower blood glucose for those with T2DM [16]. It was found to be very effective in lowering LDL blood cholesterol [36] reducing CV morbidity and mortality but has minimum effect in reducing blood glucose; it increases blood triglyceride and may cause acute pancreatitis [23]. It also causes constipation. The drug is used infrequently in the US and Europe [3].

1.1.8. D2 DOPAMINE RECEPTOR AGONIST: The dopamine agonist bromocriptine is only available in the US as an antihyperglycemic agent [37]. It acts by activating brain D2 dopamine receptors, increases insulin sensitivity by unknown mechanisms, reduces hepatic gluconeogenesis and lowers plasma glucose level [16,23]. A rapid-release form has been approved by the FDA in 2010, as an adjunct to diet and exercise to improve glycemic control in adults with T2DM [6]. Bromocriptine has very modest effect on lowering blood glucose[3]. Side effects are dizziness, syncope, nausea, fatigue and rhinitis [7]. Bromocriptine is predominantly metabolized in the liver and only 2-6% appears in the urine [38]. No studies evaluating the safety of this medicine in patients with reduced GFR have been performed; therefore it should be used with caution in patients with CKD [38]. Bromocriptine is not licensed in Europe for the treatment of T2DM. The long term safety remains unknown [7].

1.1.9. SODIUM GLUCOSE COTRANSPORTER TYPE 2 (or sodium-glucose linked transporter, SGLT2) INHIBITORS: SGLT-2 inhibitors are the most advanced new oral antidiabetic drugs that lower HbA1C by increasing glycosuria and lead to a moderate weight loss [18]. Two drugs recently approved for use in this class are dapagliflozin and canagliflozin for the treatment of T2DM as an adjunct to diet and exercise as monotherapy, as initial therapy with metformin, or as an add-on to other oral glucose-lowering agents, including metformin, pioglitazone, SUs, DPP-4 inhibitors, and insulin [39,40]. Dapagliflozin acts by selectively inhibiting SGLT2 in the proximal convoluted tubule, preventing renal tubular reabsorption of glucose, leading to glycosuria in a glucose dependant fashion and lowering plasma glucose levels while sparing insulin secretion and function [39,40]. Therapy with dapagliflozin also results in a mild osmotic-diuretic effect that may account for decrease in total body weight and blood pressure. Dapagliflozin produces a sustained, dose-dependent reduction in plasma glucose levels both fasting and postprandial, while simultaneously improving insulin secretion and sensitivity[40]. Dapagliflozin was associated with increased risk of genital and urinary-tract infections in most studies [41,42]. Dapagliflozin does not produce hypoglycemia. Clinical trials have focused on the 1–10 mg/day range based on near maximal blood glucose effects and acceptable tolerability. Dapagliflozin is dosed once daily without regard to meals, has relatively long half-life and insulin-independent mechanism of action [40]. There is some concern for its use in the elderly and those at risk of hypotension. However the long-term safety and efficacy data for dapagliflozin are still lacking. The FDA approved first, canagliflozin, for clinical use in March 2013. Dapagliflozin is the second SGLT2 inhibitor to be approved by the FDA on January 8, 2014 [39]. However dapagliflozin was the first SGLT2 approved in November 2012 by the EMA and is already being used in 38 countries, including those of the European Union (EU) and Australia [43]. Canagliflozin was approved by EMA in September 2013 for use in EU.

1.2   Parenteral or injection therapies
1.2.1. INSULIN: Due to the progressive β-cell dysfunction that characterizes T2DM, insulin replacement therapy is frequently required [44]. Insulin is the oldest of the currently available medications and is the most effective at lowering glycemia. Insulin can, when used in adequate doses, decrease any level of elevated HbA1c to the therapeutic goal. Unlike the other blood glucose–lowering medications, there is no maximum dose of insulin beyond which a therapeutic effect will not occur. Insulin also has no restrictions for use in patients with liver or renal impairment and is indeed the preferred choice in those with advanced disease. Intensive insulin therapy has a key part of improved glycemia and better outcomes, but with weight gain and risk of hypoglycemia. Insulin therapy requires more frequent monitoring. Other concerns about insulin therapy, but are poorly understood include the possibility of an increased incidence of some cancers and an increase in long-term mortality and CV events in patients with diabetes who have had severe hypoglycemic episodes [45].

a. Human (conventional) insulins which are currently used are (a) short acting (or regular insulin), (b) intermediate acting (Neutral Protamin Hagedorn or NPH insulin), and (c) premixed human insulin (mixture of regular and NPH insulin).

b. The development of amino acid substitutions of the human insulin molecule has led to the creation of analog insulins that can provide more physiologic glycemic control [46]. Analog insulins currently used are (a) rapid acting analog insulin (Lispro, Aspart & Glulisine); (b) long acting analog insulin (Detemir and Glargine) and (c) premixed analog insulin (mixture of Lispro & Lispro Protamine; Aspart & Aspart Protamine, etc). (d) In October 2012 the EMA has granted marketing and authorization to 2 new antidiabetic products, ultra-long-acting insulin degludec and a combination agent containing insulin degludec with insulin aspart. The approvals cover all 27 EU member states [47]. Both drugs are under regulatory review in the US and other major markets [47]. The analog insulin corresponds with the physiological secretion of insulin after meal (using rapid acting analogs) and in basal conditions (using long acting analogs). Insulin analogs possibly are associated with slightly less weight gain, but are more expensive [48]. The rapidly acting insulin analog when injected subcutaneously are absorbed very rapidly, and the patient can eat his meal immediately without waiting for 30 minutes, so rapid acting insulin analogs are injected immediately before food. They result in better postprandial glucose control than the less costly human regular insulin. Because it maintains a relatively constant concentration/time profile over 24 hours with no pronounced peak, insulin glargine has a duration of action that allows once-daily dosing. Insulin analogs with longer, nonpeaking profiles decrease the risk of hypoglycemia modestly compared with NPH; rapid acting insulin analogs also reduce the risk of hypoglycemia compared with regular insulin [49,50].

i. INSULIN DEGLUDEC (IDeg): IDeg is new ultra-long acting analog insulin and a basal insulin that has no amino acid substitutions in its primary structure compared with human insulin. There are two modifications to the B chain: threonine, (an amino acid) at B30 is deleted and an amino acid linker and a fatty acid are added to the lysine at position B2951. IDeg has retained the amino acid sequence of human insulin apart from deletion of residue B30. To accomplish the long action profile, a fatty acid (hexadecanedioic acid) has been coupled to the lysine at position B29 via a short glutamic acid spacer. Its unique mechanism of action is based on multihexamer formation after subcutaneous injection which is slowly absorbed into the circulation. This mechanism provides a long, stable, and consistent release of IDeg [51,52]. It has been designed to meet the need for a flat, consistent basal insulin that provides steady coverage for more than 24 hours and from day to day for all patients, with the primary advantage being reduced hypoglycemia, particularly at night. It has a half-life of 25 hours, which is twice as long as the half-life of currently available basal insulins, and with a 42 hour duration of effect [47]. In addition, because of its long half-life, the dosing regimen allows for flexibility if a patient misses or delays a dose [47]. IDeg administered once daily was found to be significantly less variable and more stable in maintaining euglycemia as compared to glargine [53]. However on occasions when administration at the same time of day is not possible, IDeg allows flexibility in the timing of insulin administration without compromising efficacy and hypoglycemia. It also has a good safety profile. Studies have shown that insulin degludec provides comparable glycemic control to insulin glargine, but lower incidence of hypoglycemic events in both type 1 and type 2 diabetic patients [54,55].

ii. INSULIN DEGLUDEC-ASPART (IDegAsp): IDegAsp is a combination agent containing insulin degludec (70%) and insulin aspart (30%). This formulation provides both basal and prandial insulin and can be used as premixed insulin. This combination is also known as degludec plus [52]. IDegAsp might be a promising treatment option for patients with type 2 diabetes who need to improve control of postprandial glucose excursions and fasting glucose levels [56]. In a 16-week, open-label trial in T2DM, insulin degludec aspart was administered before the evening meal and dose-titrated to an FPG target of 4.0–6.0 mmol/L. Once-daily degludec aspart was found to be safe, well tolerated, and efficacious with low rates of hypoglycemia, and better post-dinner plasma glucose control [57]. A recently published study assessed the efficacy and safety of once-daily dose in combination with mealtime insulin aspart in people with T1DM in a 16-week, randomized, open-label trial. This trial found degludec to be safe and well tolerated, while providing comparable glycemic control to glargine at similar doses, with reduced rates of hypoglycemia [58]. Another study also demonstrated the efficacy and tolerability of IDegAsp, combined with additional meal-time insulin aspart in the treatment of type 1 diabetes [59]. IDegAsp in basal-bolus therapy with additional insulin aspart at meal-times has shown to improve overall glycemic control.

1.2.2. GLP-1 ANALOGS: The injectable GLP-1 receptor agonists mimic the effects of endogenous GLP-1, thereby stimulating pancreatic insulin secretion in a glucose-dependent fashion, suppressing pancreatic glucagon output, slowing gastric emptying, and decreasing appetite [60]. Their main advantage is weight loss, which is modest in most patients but can be significant in some. A limiting side effect is nausea and vomiting, particularly early in the course of treatment. Concerns regarding an increased risk of pancreatitis remain unresolved [3]. Exenatide and liraglutide are currently available GLP-1 analogs. They have to be given daily by subcutaneous injection (exenatide needs to be given twice daily: 5 mcg sc bid for one month, then ↑ to 10 mcg bid, and liraglutide once daily: initially 0.6mg, increased at 1-2 weeks by 0.6mg to a maintenance dose of 1.2 - 1.8 mg sc once daily). Exenatide was approved for use in the US in 2005 [25]. Exenatide has been seen to be associated with acute pancreatitis; however, the number of cases is very small and whether the relationship is causal or coincidental is not clear at this time. Liraglutide was approved by FDA in January, 2010. Liraglutide has been seen to cause medullary carcinoma of the thyroid in rodents; however, no such tumors have been observed in humans taking this drug [61]. Liraglutide use is contraindicated in patients with a personal or family history of medullary thyroid carcinoma or in patients with multiple endocrine neoplasia syndrome. Exenatide is contraindicated in stage 4–5 CKD (GFR <30 mL/min) as it is renally eliminated [62,63]; Liraglutide is fully degraded elsewhere in the body, and the kidneys are not a major organ of elimination [3,64]. However, the safety of liraglutide on long term use is not established and the manufacturer recommends avoiding this medicine when GFR is <60 mL/min/1.73 m2 [65]. In patients with mild hepatic disease, incretin-based drugs can be prescribed, except if there is a coexisting history of pancreatitis [3]. Substantial falls were seen in systolic and diastolic blood pressures and in total cholesterol levels in patients with diabetes mellitus by GLP-1 related therapies [66]. The GLP-1 analogs are very expansive and their long term safety profile remains unknown.

1.2.3. AMYLIN ANALOGS: Pramlintide, a synthetic analog of amylin and was approved by the FDA in March 2005 for use as adjunctive therapy with regular or rapid-acting insulin analogs usually in T1DM. Pramlintide inhibits glucagon secretion in a glucose-dependent fashion, slows gastric emptying and stimulates satiety thereby decreasing appetite [67]. It predominantly decreases postprandial glucose excursions and is associated with weight loss. The disadvantage of amylin analogs are that they need to be given subcutaneously before meals, are expansive, have frequent gastrointestinal side effects and their long term safety is unknown[5]. Use of pramlintide is not recommended for patients with CKD stage 4 or greater [38].

IV. ANTIDIABETIC DRUGS IN PREGNANCY & LACTATION

Regular or rapid-acting insulin analogs are the preferred treatment for postprandial hyperglycemia in pregnant women. Basal insulin needs can be provided by using long-acting or intermediate acting insulin (e.g. NPH; FDA pregnancy category B) [68]. The efficacy and safety of insulin have made it the standard for treatment of diabetes during pregnancy. However, oral agents like glibenclamide and metformin, have been gaining popularity. Trials have shown these 2 drugs to be effective, and no evidence of harm to the fetus has been found, although the potential for long-term adverse effects remains a concern [23,69]. Among the oral antidiabetic agents, metformin and acarbose are classified as category B and all others as category C. Although insulin is the preferred treatment approach, metformin and glibenclamide have been shown to be effective alternatives and without adverse effects in some women [68]. Approximately 15-25% of neonates delivered from women with diabetes during gestation develop hypoglycemia during the immediate newborn period [70]. Unrecognized postnatal hypoglycemia may lead to neonatal seizures, coma, and brain damage. Current recommendations for infants of diabetic mothers—the most critical metabolic problem for whom is hypoglycemia—include the employment of frequent blood glucose checks and early oral feeding (ideally breast milk) when possible, with infusion of intravenous glucose if oral measures prove insufficient. Insulin requirements drop immediately after delivery, and a dose adjustment will be needed to allow for the eating patterns of the breastfeeding mother. Metformin and possibly glibenclamide may be used [71]. The medications should be reviewed taking into consideration the potential risks associated with any transfer into the milk. The baby should, however, be monitored for signs of hypoglycemia. The very limited amounts of metformin observed in breast milk are highly unlikely to lead to substantial exposure in the breastfed baby. Metformin can be considered a safe medication for the treatment of T2DM in a breastfeeding mother [72].

V. RECENT GUIDELINES FOR PHARMACOTHERAPY OF T2DM

5.1 Several treatment guidelines and algorithms have been recently developed by the expert committee of different organizations that differ considerably in their approach, in terms of target values of glucose control, and strategies for drug choice despite the same objectives.

5.2 The American Diabetes Association (ADA) & European Association for the Study of Diabetes (EASD) [25] consensus statement for the treatment of nonpregnant patients with T2DM highlights intervention at the time of

diagnosis with metformin in combination with lifestyle changes and continuing timely augmentation of therapy with additional agents from a different class (including early initiation of insulin therapy) as a means of achieving and maintaining recommended levels of glycemic control (i.e. HbA1c <7% for most patients). The ADA/EASD [3] emphasized that all treatment decisions, where possible, should be made with the patient, focusing on his/her preferences, needs, and values. Importance has been provided to individualize treatment targets. Their recommendation were that more stringent HbA_{1c} targets (e.g. 6.0–6.5%) might be considered in selected patients (with short disease duration, long life expectancy, no significant CVD) if this can be achieved without significant hypoglycemia or other adverse effects of treatment [3,23]. Conversely, less stringent HbA1c goals—e.g., 7.5–8.0% or even slightly higher—are appropriate for patients with a history of severe hypoglycemia, limited life expectancy, advanced complications, extensive co-morbid conditions and those in whom the target is difficult to attain despite intensive self-management education, repeated counseling, and effective doses of multiple glucose-lowering agents, including insulin [3,23,73].

5.3 The pharmacologic recommendations made by American Association of Clinical Endocrinologists (AACE) /American College of Endocrinology (ACE) treatment algorithm for the management of adult, nonpregnant patients with T2DM are stratified by baseline HbA1c [74]. Upon diagnosis, monotherapy is recommended for patients with HbA1c <7.5%, dual therapy for patients with HbA1c 7.6%-9%, and insulin for patients with HbA_{1c} >9%. Metformin is designated as the preferred first-line choice in both monotherapy and dual therapy regimens [74]. The AACE/ACE guidelines recommend a target HbA1c level of 6.5% or less in general, but recognize the need for individual treatment plans and emphasize personalized glycemic goals [68]. Blood glucose targets should be individualized and take into account life expectancy, duration of disease, presence or absence of other complications, cardiovascular risk factors, co-morbid conditions and psychological, social, and economic status as well as risk for development of and consequences from severe hypoglycemia [68].

5.4 International Diabetes Federation (IDF) [75] recommends glycemic target value for HbA1c of <7%. IDF however, concentrates on the role of postprandial hyperglycemia and calls for HbA1c target value of 7% [75,76] and advocates the target for postmeal glucose 9.0 mmol/L (160 mg/dl) as long as hypoglycemia is avoided.

5.5 The American College of Physicians (ACP) guidelines recommend that clinicians add oral pharmacologic therapy with metformin (unless contraindicated) in patients diagnosed with T2DM when lifestyle modifications, including diet, exercise, and weight loss, have failed to adequately improve hyperglycemia [77].

VI. DISCUSSION

6.1 A large amount of information is available on the efficacy of the various antidiabetic regimens used to achieve long-term glycemic control in patients with T2DM. The results from the "UK Prospective Diabetes Study" (UKPDS) [78] and the "A Diabetes Outcome Progression Trial" (ADOPT) [29] showed quite clearly that a patient's response to any one specific antidiabetic agent decreases with time. The authors of these studies suggested that complex regimens with multiple agents that have different mechanisms of action will be required to maintain target HbA_{1c} goals in the long term [29,78]. Selection of the individual agents should be made on the basis of their glucose-lowering effectiveness, and overall other characteristics including the individual patient.

6.2 It is evident that lifestyle changes remain the foundation of treatment program of T2DM. All updated guidelines specify that glycemic goals should be individualized and all advocate lifestyle modifications and metformin as first-line therapy, though they differ in their subsequent recommendations [3,25,68,74-77]. Metformin is cheaper than most other pharmacologic agents, has better effectiveness, and is associated with fewer adverse effects. Patient having moderate hyperglycemia or in whom lifestyle changes are anticipated to be unsuccessful should be promptly started with oral antidiabetic agent preferably with metformin at diagnosis, which can later be modified or possibly discontinued if lifestyle changes are successful3. If glycemic targets are not achieved by monotherapy (metformin) alone then one can proceed to dual therapy, and further advancing to triple therapy by combining drugs from different classes having different mechanism of actions which may include basal insulin. Medication choice is based on patient and drug characteristics like susceptibilities to side effects, dosing frequency, potential for weight gain and hypoglycemia; and presenting comorbidities [3].

6.3 The UKPDS demonstrated that the great majority of patients with T2DM will eventually require insulin due to the progressive loss of pancreatic β-cell function and that early addition of insulin can significantly improve glycemic control [79]. Patients with T2DM requiring insulin therapy can be successfully treated with basal insulin combined with oral drugs. Intermediate (NPH) or long-acting analog insulins can be administered as basal therapy [3,46]. Basal insulin, added to metformin is a particularly effective means of lowering glycemia

while limiting weight gain [80]. Consideration should be given to the addition of prandial or mealtime insulin coverage when significant postprandial glucose excursions occur (basal bolus or basal plus mealtime insulin). Premixed human insulin or analog insulin commonly used twice daily can control both fasting and postprandial glucose and preferred by most of the patient. Short-acting and intermediate-acting insulin (NPH) mixed by patient, given before breakfast and the evening meal, is the simplest regimen and is still commonly used because it allows greater flexibility in dosing (split dose regimen). Importantly, most patients with T2DM maintain some endogenous insulin secretion even in late stages of disease. Accordingly, the more complex and intensive strategies of type 1 diabetes are not typically necessary [81].

VII. CONCLUSION

7.1 Medical therapy for patients with T2DM has improved considerably during the past decade. A substantial percentage of patients with T2DM can achieve target glycemic control with minimal adverse effects from their medical treatment. Obviously, the choice of glycemic goals and the medications used to achieve them must be individualized for each patient, balancing the potential for lowering HbA1c and anticipated long-term benefit with specific safety issues, as well as other characteristics of regimens, including tolerability, ease of use, long-term adherence, expense, and the nonglycemic effects of the medications.

7.2 While the existing insulin analogues have certain advantages and are able to achieve glycemic control in a safe and well-tolerated manner, currently available basal insulin analogs have some limitations. Newer basal insulins such as IDeg can be used singly or in formulation with aspart insulin to provide glycemic control. IDeg has the potential to emerge as an ideal basal insulin. It may be an attractive therapeutic alternative to the other basal insulins, due to less pharmacodynamic variability, a longer duration of action and, less hypoglycemic events. IDeg allows flexibility in the timing of insulin administration without compromising efficacy.

7.3 SGLT-2 inhibitors are the most advanced new oral antidiabetic agents that lower HbA1c by increasing glycosuria and lead to a moderate weight loss. SGLT2 inhibitors may be a suitable for T2DM patients who do not tolerate metformin, or unable to sustain glucose lowering effect on metformin, individuals who like to see weight loss, and those with good renal function.

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