Review Article

Update on Pharmacotherapy for Type 2 Diabetes

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Abstract:

Patients with type 2 diabetes mellitus (T2DM) are usually treated with pharmacologic agents in combination with lifestyle modification. Recently new antidiabetic drugs have been introduced to supplement the older therapies, such as insulin, sulfonylureas, and metformin, thereby increasing the number of treatment options by the practitioners and patients which has heightened uncertainty regarding the most appropriate means of treating this widespread disease. The development of antidiabetic agents in this millennium, like insulin analogs, incretin-based therapies {Dipeptidyl Peptidase-4 (DPP-4) inhibitors & Glucagon like peptide-1 (GLP-1) analogs}, colesevelam, bromocriptine and pramlintide has also led to treatment strategies that enable many patients with T2DM to achieve target HbA1c levels (<7.0%). Pharmacologic treatment of patients with T2DM is limited not only by the effectiveness or adverse effects of the agent but also by the cost, patient's preferences, needs, and values. This review article discusses the current pharmacological agents, their latest successes, demerits and limitations in the treatment of patients with T2DM. This article also reviews the different updated guidelines, treatment algorithms, and recommendations provided for the management of T2DM by expert committees of different associations and federations. In June 2012, American Diabetes Association (ADA) & European Association for the Study of Diabetes (EASD) has described patient centered approach in the management of T2DM and stressed importance to individualize treatment targets. More stringent HbA1c targets (e.g., 6.0-6.5%) might be considered in selected patients. Conversely, less stringent HbA1c goals-e.g., 7.5-8.0% or even slightly higher-are appropriate for some other patients. International Diabetes Federation (IDF) document in 2011, however, concentrates on the role of postprandial hyperglycemia and calls also for HbA1c target value of 7.0%. 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. Metformin is cheaper than most other pharmacologic agents, has better effectiveness, and is associated with fewer adverse effects; of note, it does not result in weight gain.

Introduction

The incidences of both type 1 and type 2 diabetes are rising. The global pandemic principally involves the T2DM which is associated with greater longevity, obesity, unsatisfactory diet, sedentary lifestyle and increasing urbanization1. An estimated 366 million people worldwide had diabetes in 2011 and this number

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is projected to reach 552 million in 2030[2]. T2DM remains a leading cause of cardiovascular (CV) disorders, blindness, end-stage renal failure, 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 (initially the introduction of meglitinides, the alfa - glucosidase inhibitors and the thiazolidinediones) reflects the increase in our understanding of the multiple targets for improving hyperglycemia. The further development of antidiabetic agents, such as insulin analogs and incretin-based therapies (DPP-4 inhibitors and GLP-1 analogs), has led to treatment strategies that enable many patients with T2DM to achieve target HbA1c levels ($\leq$7.0%)[4]. Other agents which have been included in the pharmacotherapy T2DM are amylin analog (pramlintide), bile acid sequestrants (colesevelam) and D2 dopamine receptor agonists (bromocriptine)[5]. Effective management strategies are of obvious importance. But glycemic management in T2DM has become increasingly complex with a widening array of pharmacological agents now available. Pharmacologic treatment of patients with T2DM is limited not only by the effectiveness of the agents but also by their adverse effects. 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 used, their latest successes, merits, demerits and limitations in the treatment of patients with T2DM. This article also reviews the different updated guidelines and algorithms provided by expert committees of ADA/EASD, IDF, American Association of Clinical Endocrinologists (AACE), and American College of Physicians (ACP).

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. Insulin resistance in muscle & liver and beta-cell failure represent the core pathophysiologic defects in type 2 diabetes and are well established early in the natural history of the disease, but T2DM does not occur in the absence of progressive beta cell failure. In addition to the muscle, liver and beta-cell, the alfa-cell (hyperglucagonemia), 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 (Figure 1)[6]. 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 beta-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[6]. Amylin is a natural hormone produced by the beta-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 beta-cells. More recently abnormalities in the incretin system (GLP-1) have been recognized in T2DM[7]. 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.

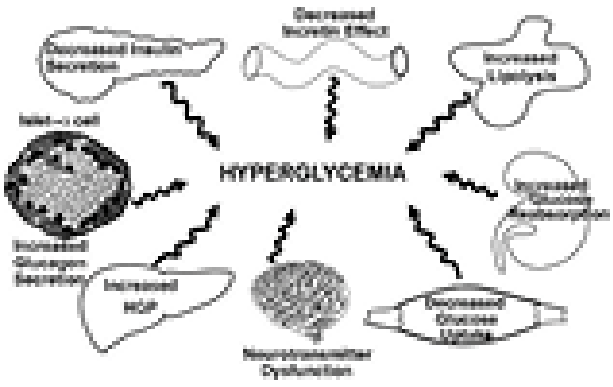


Figure 1: The ominous octet-from "Diabetes 2009" 6.

Antidiabetic drugs

Currently, 11 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 US[8]. 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, alfa-glucosidase inhibitors (AGIs), pramlintide, exenatide and prandial insulins); and with still others that do both {thiazolidinediones (TZDs), 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, AGIs, DPP-4 inhibitors, colesevelam, and bromocriptine[9,10,11].

Oral agents

Oral agents that improve insulin secretion by the pancreatic beta cells are known as insulin secretagogs and are sulfonylureas and meglitinides. 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. Metformin predominately acts by reducing hepatic glucose output lowering fasting hyperglycemia, whereas TZDs mainly by improving insulin sensitivity in the skeletal muscles. The AGIs delay carbohydrate absorption in the gut by selectively inhibiting intestinal alfa-glucosidase. 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[5].

a. BIGUANIDE: The only drug used now in this class in most of the world is metformin. 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. Renal dysfunction is considered a contraindication to metformin use because it may increase the 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 $\geq$133 µmol/L ($\geq$1.5 mg/dL) in men or 124 µmol/L $\geq$(1.4 mg/dL) in women[3]. However, recent studies have suggested that metformin is safe unless the estimated glomerular filtration rate falls to <30 ml/min with dose reduction advised at 45 mL/min[12,13,14]. In UK treatment with metformin is withdrawn when creatinine is higher than 150 µ mol/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[15]. 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[16].

b. SULFONYLUREAS (SUs): 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 to be used during acute CV events. Glibenclamide which has a prolonged duration of action should not be used in renal failure1,3. In addition, studies have demonstrated a secondary failure rate by SUs that may exceed other drugs, ascribed to an exacerbation of islet dysfunction[17]. 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[13].

c. MEGLITINIDES: The meglitinides 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 HbA1c than repaglinide when used as monotherapy or in combination therapy[13]. These drugs are associated with hypoglycemia and weight gain. Meglitinides can be used in liver dysfunction3. Repaglinide and nateglinide do not undergo significant renal clearance but caution is imperative at more severe degrees of renal dysfunction3.

d. 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 hypoglycemia, , HDL cholesterol and 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[3,15]. In addition both the drugs have increased risk of fracture particularly in women. TZDs increase peripheral (subcutaneous) adipose tissue mass with some reduction in visceral fat[13]. In July 2007 a study published in NEJM shows 40% increase risk of CV events and death among users of rosiglitazone[18]. The European Medicines Agency (EMA) is phasing out the use of rosiglitazone. In September 2010 FDA significantly restricts access to rosiglitazone. FDA decision: rosiglitazone will be available to new patients only if they are unable to achieve glucose control on other medications and are unable to take pioglitazone, the only other drug in this class[19]. Current users of rosiglitazone who are benefiting from the drug will be able to continue using the medication if they choose to do so. Pioglitazone has recently been associated with a possible increased risk of bladder cancer and has drawn attention[20]. In June 2011-France and Germany suspended use of pioglitazone. FDA & EMA is recommending that T2DM patients with current bladder cancer, a history of the disease, or uninvestigated macroscopic hematuria, should not be prescribed pioglitazone.

e. 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. The AGIs should not be used with renal dysfunction.

f. 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[13]. The DPP-4 inhibitors reduces postprandial glucose excursion. They do not cause hypoglycemia when used as monotherapy. 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. 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. Concerns regarding an increased risk of pancreatitis remain unresolved[3]. In patients with mild hepatic disease, incretin-based drugs can be prescribed, except if there is a coexisting history of pancreatitis3. Among the DPP-4 inhibitors, sitagliptin, vildagliptin, and saxagliptin share prominent renal elimination. In the face of advanced CKD, dose reduction is necessary. The DPP-4 inhibitors are expansive and their long term safety profile remains unknown[5].

g. BILE ACID SEQUESTRANT: 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, but unknown mechanism of lowering blood glucose for those with T2DM. It was found to be very effective in lowering LDL blood cholesterol reducing CV morbidity and mortality but has minimum effect in reducing blood glucose; it increases blood triglyceride and may cause acute pancreatitis[5]. It also causes constipation. The drug is used infrequently in the US and Europe.

h. DOPAMINE 2 AGONIST: The dopamine agonist bromocriptine is available in the US as an antihyperglycemic agent. It activates brain D2 dopamine receptors to lower plasma levels of glucose[5]. It has been approved by the FDA as an adjunct to diet and exercise to improve glycemic control in adults with T2DM. Bromocriptine has very negligible effect on lowering blood glucose. Side effects are dizziness, syncope, nausea, fatigue and rhinitis.

Parentral or injection therapies

a. INSULIN: Insulin is the oldest of the currently available medications and, therefore, the treatment with which we have the most clinical experience. It is also 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. Due to the progressive beta-cell dysfunction that characterizes T2DM, insulin replacement therapy is frequently required[21]. Importantly, most patients 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[22]. 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 cardiovascular events in patients with T2DM who have had severe hypoglycemic episodes[23].

i. Human (conventional) insulins which are currently used are short acting (regular insulin), intermediate acting (NPH insulin), and premixed human insulin (mixture of regular and NPH insulin).

ii. Analog insulins currently used are rapid acting analog insulin (lispro, aspart & glulisine); long acting analog insulin (detemir and glargine) and premixed analog insulin (mixture of lispro & lispro protamine; aspart & aspart protamine, etc). Insulin analogs have been used since the start of the new millennium. The analog insulin corresponds with the physiological secretion of insulin after meal (using rapid acting analogs) and in basal conditions (using long acting analogs). 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. Insulin analogs with longer, nonpeaking profiles decrease the risk of hypoglycemia modestly compared with NPH; and rapid acting insulin analogs also reduce the risk of hypoglycemia compared with regular insulin[24,25]. Insulin analogs possibly are associated with slightly less weight gain, but are more expensive[26].

Basal insulin, usually with intermediate (NPH) or long-acting analog insulins added to metformin is a particularly effective means of lowering glycemia while limiting weight gain[27]. Patients with T2DM requiring insulin therapy can also be successfully treated with basal insulin alone. Some patient, because of progressive diminution in their insulin secretory capacity, will require prandial insulin therapy with regular or rapid acting analog insulin (basal bolus or basal plus mealtime insulin) and considered when significant postprandial glucose excursions occurs. 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 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).

b. GLP-1 ANALOGS: Exenatide and liraglutide are currently available GLP-1 analogs. They have the advantage of inducing weight loss in most patients. 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 200513. Use of GLP-1 analog is associated with nausea and vomiting; although these symptoms generally lessen with continued treatment. 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[28]. Liraglutide use is contraindicated in patients with a personal or family history of medullary thyroid carcinoma or in patients with multiple endocrine neoplasia syndrome. For the GLP-1 analogs exenatide is contraindicated in stage 4-5 CKD (GFR <30 mL/min) as it is renally eliminated; the safety of liraglutide is not established in CKD though pharmacokinetic studies suggest that drug levels are unaffected as it does not require renal function for clearance[3]. In patients with mild hepatic disease, incretin-based drugs can be prescribed, except if there is a coexisting history of pancreatitis3. 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[29]. The GLP-1 analogs are very expansive and their long term safety profile remains unknown.

c. AMYLIN ANALOGS: Pramlintide is a synthetic analog of amylin. It is administered subcutaneously before meals and slows gastric emptying, inhibits glucagon production in a glucose-dependent fashion, and predominantly decreases postprandial glucose excursions. Pramlintide was approved by the FDA in March, 2005 for use as adjunctive therapy with regular insulin or rapid-acting insulin analogs. In studies, pramlintide-treated patients achieved lower blood glucose levels and experienced weight loss. The disadvantage of amylin analogs are that they need to be given parentrally, are expansive, have frequent gastrointestinal side effects and their long term safety is unknown[5].

Review of recent guidelines and algorithms for treatment of T2DM

Several treatment guidelines and algorithms for patients with T2DM 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.

a. The ADA/EASD (published in Diabetes Care Jan 2009), issued a consensus statement on the management of hyperglycemia in the nonpregnant adult (Figure 2) to help guide health care providers in choosing the most appropriate interventions for their patients with T2DM[13].

Highlights include 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). In the setting of severely uncontrolled diabetes, defined as fasting plasma glucose levels >13.9 mmol/l (250 mg/dl), random glucose levels consistently above 16.7 mmol/l (300 mg/dl), HbA1c above 10%, or the presence of ketonuria, or as symptomatic diabetes with polyuria, polydipsia and weight loss, insulin therapy at the outset in combination with lifestyle intervention is the treatment of choice[13]. After symptoms are relieved and glucose levels decreased, oral agents can often be added and it may be possible to withdraw insulin, if preferred [13].

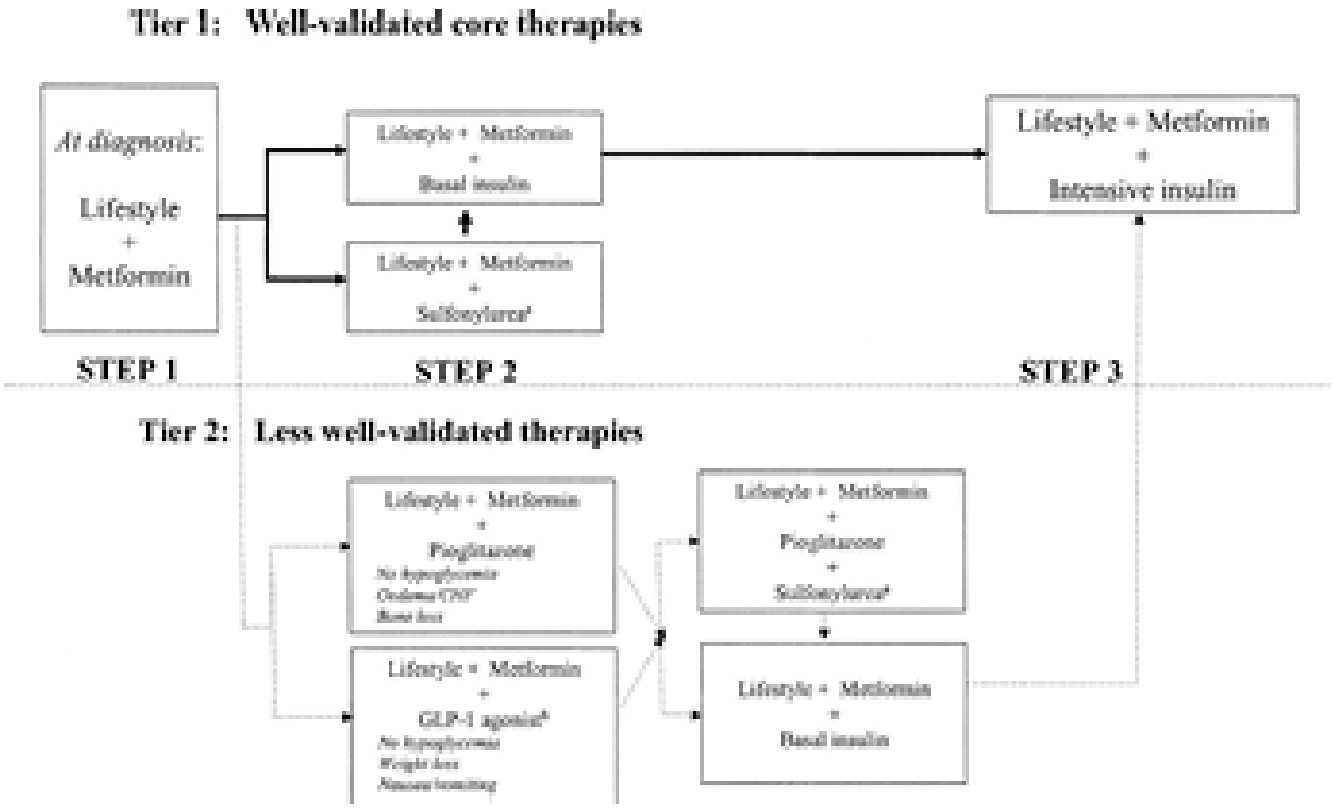


Figure 2: Algorithm for the metabolic management of T2DM published in Diabetes Care Jan 200913.

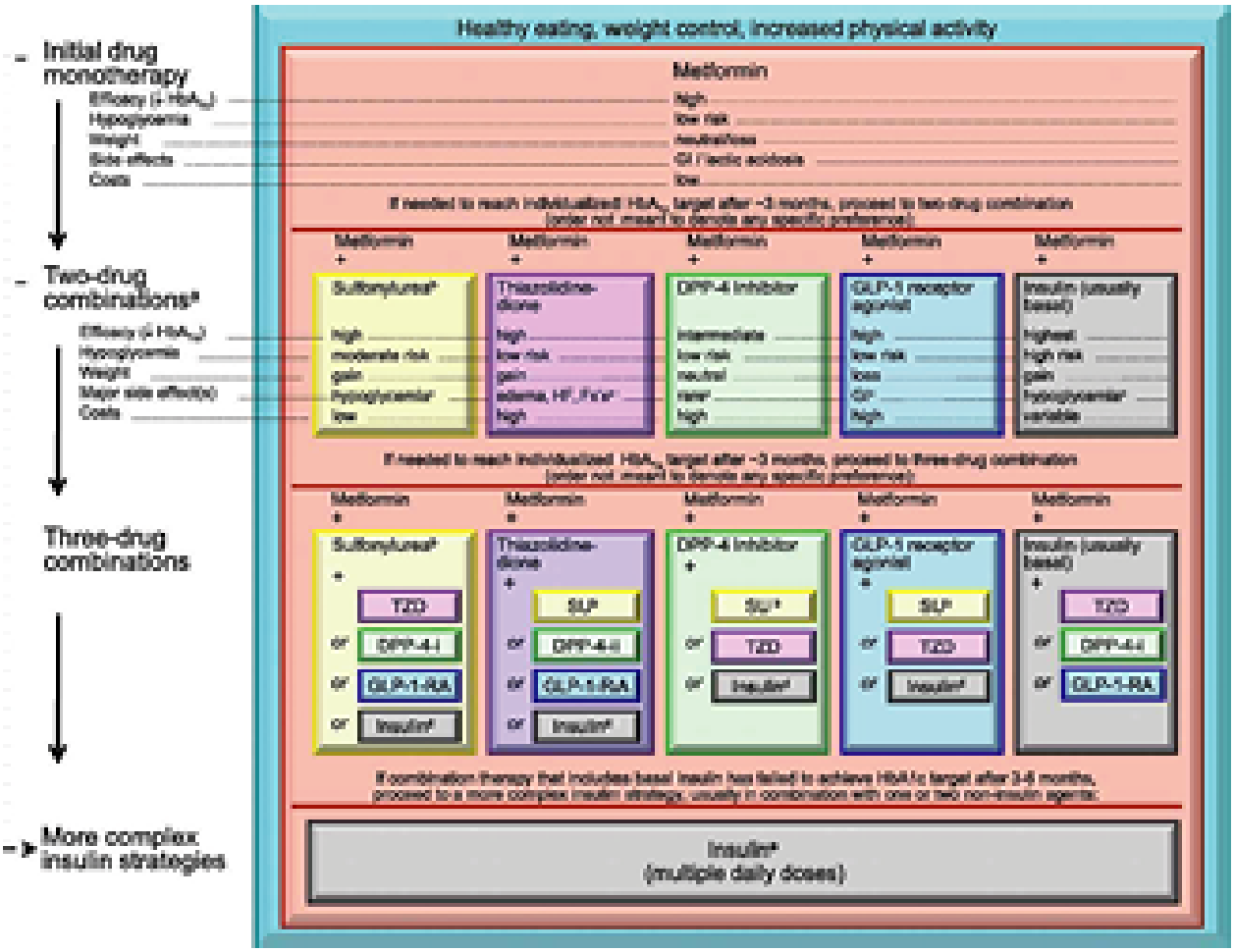
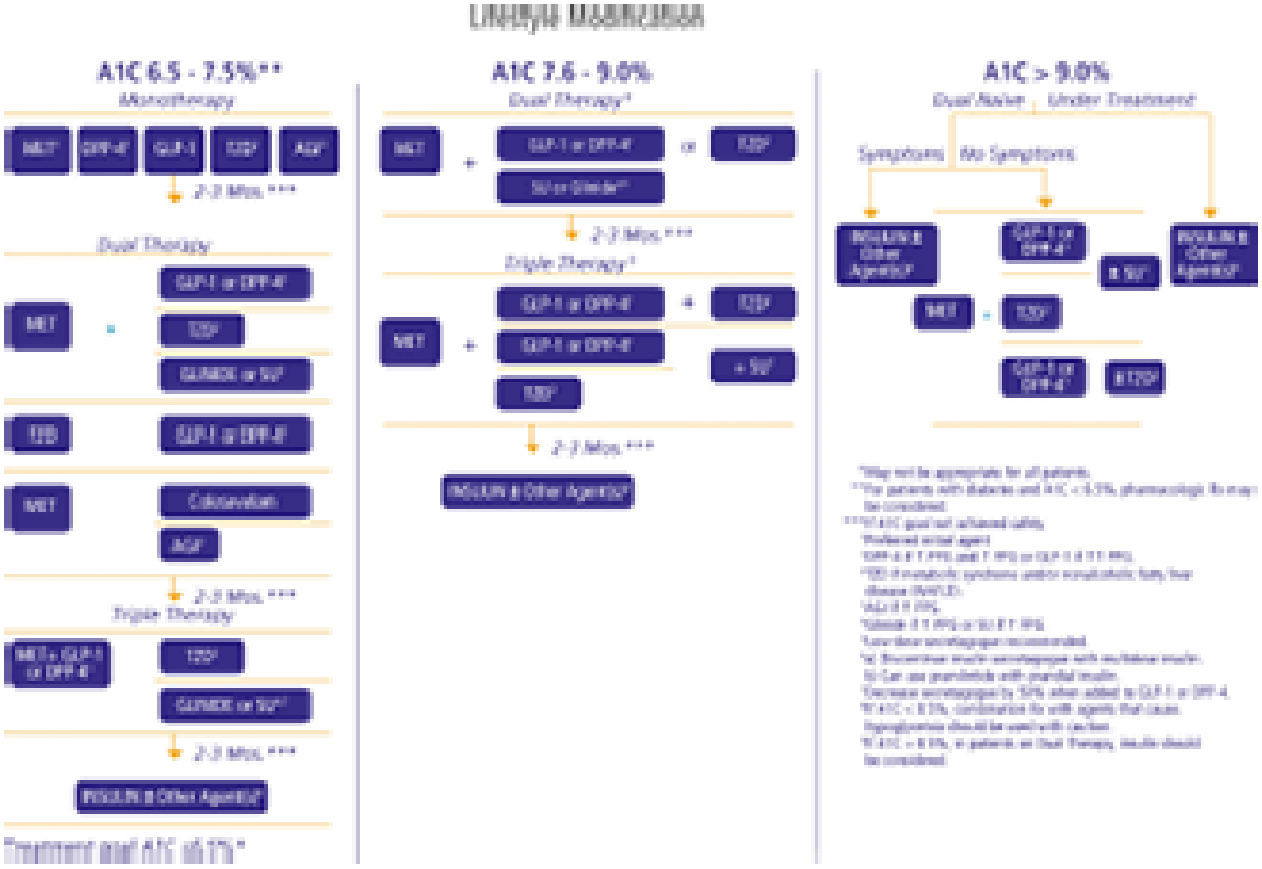


Figure 3: Antihyperglycemic therapy in T2DM: general recommendations. Published in Diabetes Care June 20123

b. The ADA/EASD guideline published in the Diabetes Care June 2012[3] highlights on the treatment decisions, to be made with the patient, focusing on his/her preferences, needs, and values (Figure 3). The previous recommendation for all patients on glycemic targets HbA1c of <7% % has also been elaborately modified. Importance has been provided to individualize treatment targets. For example, the blood sugar goal for a young, otherwise healthy patient should be lower (an HbA1c of 6-6.5 percent) than that of an older patient with other health problems (HbA1c 7.5-8 percent)[3]. At diagnosis, highly motivated patients with HbA1c already near target (e.g. <7.5%) could be given the opportunity to engage in lifestyle change for a period of 3-6 months before embarking on pharmacotherapy. Those with moderate hyperglycemia or in whom lifestyle changes are anticipated to be unsuccessful should be promptly started on an antihyperglycemic agent (usually metformin) at diagnosis, which can later be modified or possibly discontinued if lifestyle changes are successful. If a patient presents with significant hyperglycemic symptoms and/or has dramatically elevated plasma glucose concentrations (e.g., >16.7-19.4 mmol/L [>300-350 mg/dL]) or HbA1c (e.g., ≥10.0-12.0%), insulin therapy should be strongly considered from the outset.



c. AACE/ACE treatment algorithm for the management of adult, nonpregnant patients with T2DM was published in Endocr Pract 2009(Figure 4)30. In order to minimize the risk of diabetes related complications, the goal of therapy is to achieve a HbA1c of 6.5% or less, with recognition of the need for individualization to minimize the risks of hypoglycemia. The AACE/ACE algorithm includes lifestyle modification as the foundation of antihyperglycemic therapy, while pharmacologic recommendations are stratified by baseline HbA1c. 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 HbA1c >9%. If the treatment goal of <6.5% is not met within 2 to 3 months, AACE recommends intensifying therapy by adding another agent from a different class. Metformin is designated as the preferred first-line choice in both monotherapy and dual therapy regimens.

d. In April 2011 the AACE released new medical guidelines for developing comprehensive care plan for management of diabetes mellitus[31]. The 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. Blood glucose targets should be individualized and take into account life expectancy, duration of disease, presence or absence of other complications, cardiovascular risk factors, comorbid conditions and psychological, social, and economic status as well as risk for development of and consequences from severe hypoglycemia.

e. IDF treatment algorithm recommends glycemic target value for HbA1c of <7% (Figure 5)[32]. IDF document released in 2011 concentrates on the role of postprandial hyperglycemia and has advocated the target for postmeal glucose 9.0 mmol/l (160 mg/dl) as long as hypoglycemia is avoided[33]. The section presents a description of the pharmacologic agents preferentially lowering postmeal plasma glucose taking into consideration locally available therapies and resources. This approach also complements the IDF treatment algorithm for people with type 2 diabetes (Figure 5).

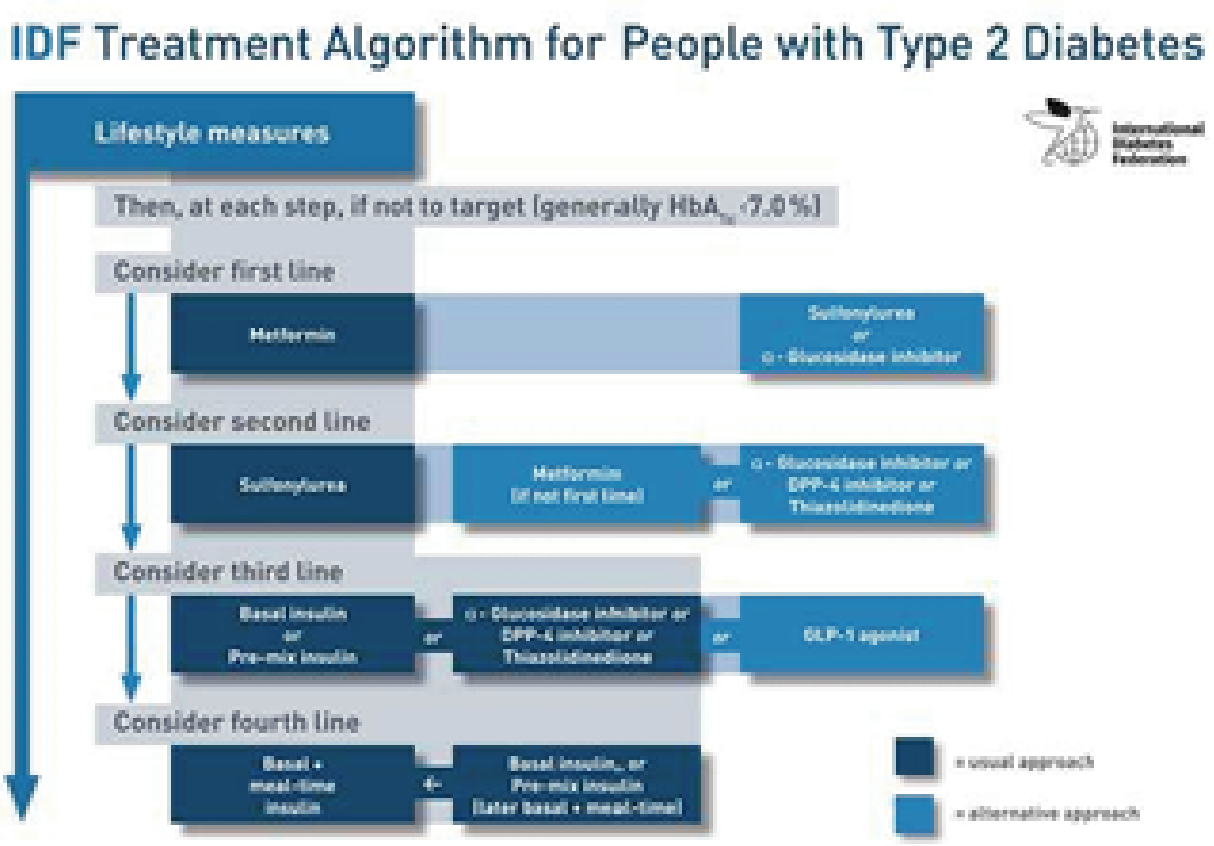


Figure 5: IDF treatment algorithm for people with T2DM 32.

f. The ACP guidelines were published in Annals of Internal Medicine 2012[8]: The ACP recommends 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. ACP also recommends that clinicians add a second agent to metformin to treat patients with persistent hyperglycemia when lifestyle modifications and monotherapy with metformin fail to control hyperglycemia.

g. Institute for Clinical Systems Improvement (ICSI) recommendations-2012[15]: Concurrent initiation of metformin with medical nutrition therapy is recommended for most patients at diagnosis. At the time of diagnosis, if patients have severe symptomatic disease, insulin should be initiated.

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 insulin (e.g. NPH; FDA pregnancy category B)[31]. 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[31]. However potential risks and benefits of oral antidiabetic agents in must be carefully weighed, recognizing that data are insufficient to establish the safety of these agents in pregnancy[5]. 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[34].

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[35].

Discussion

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)[36] and the A Diabetes Outcome Progression Trial (ADOPT)[17] 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 HbA1c goals in the long term[17,36]. Selection of the individual agents should be made on the basis of their glucose-lowering effectiveness, and overall other characteristics including the individual patient.

The primary goal of chronic treatment of T2DM is to reduce the incidence of microvascular and macrovascular complications by adequate and chronic glycemic control. The mean level of HbA1c is a measure of chronic glycemic control. The ADA's "Standards of Medical Care in Diabetes" in 2011 recommends lowering HbA1c to <7.0% in most patients to reduce the incidence of microvascular disease[37]; ideally, fasting and premeal glucose should be maintained at <7.2 mmol/L (<130 mg/dL) and the postprandial glucose at <10 mmol/L (<180 mg/dL). In June 2012, ADA/EASD have developed and promoted a new, patient-centered guideline for glycemic management in T2DM. They 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 HbA1c 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[3,5]. 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 comorbid 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[3,5,38]. IDF document, however, concentrates on the role of postprandial hyperglycemia and calls for HbA1c target value of 7% [32,33] and advocates the target for postmeal glucose 9.0 mmol/l (160 mg/dl) as long as hypoglycemia is avoided The new guidelines by AACE/ACE in 2011 recognize the need for individual treatment plans and emphasize personalized glycemic goals. The guidelines recommend a blood glucose target of an HbA1c level of 6.5% or less in general, if it can be achieved safely[31]. ADA & EASD consensus statements in 2009 suggested intervention at the time of diagnosis of T2DM with metformin in combination with lifestyle changes unless metformin is contraindicated[13]. But in June 2012, they advocates lifestyle changes for newly diagnosed patients with T2DM who are highly motivated with HbA1c already near target (e.g. <7.5%)[3].

Therefore it is evident that lifestyle changes remain the foundation of treatment program of T2DM. Metformin is considered as initial drug for the treatment of T2DM by most of the updated guidelines. It 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 successful[3]. 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. Choice is based on patient and drug characteristics like susceptibilities to side effects, potential for weight gain & hypoglycemia and comorbidities. Patients with T2DM requiring insulin therapy can be successfully treated with basal insulin alone. It is usually prescribed in conjunction with one to two noninsulin agents. Consideration should be given to the addition of prandial or mealtime insulin coverage when significant postprandial glucose excursions occur. Progression from basal insulin to a twice-daily premixed insulin-could also be considered. 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[3].

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 side effects, tolerability, ease of use, long-term adherence, expense, and the nonglycemic effects of the medications.

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