Review Article

Pathogenesis and Glycemic Management of Type 2 Diabetes Mellitus: A Physiological Approach

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Abstract

Type 2 diabetes (T2DM) is an incompletely understood chronic, progressive multifactorial disease with insulin resistance and decreased β-cell function playing dominant roles in its genesis. The worldwide incidence of the disease is rapidly increasing to pandemic proportions. The increase in incidence of T2DM is attributable to changes in lifestyle, diet and obesity, but other causes remain to be defined. The disease is a major cause of early mortality due to atherosclerosis and cardiovascular disease (CVD), and is the leading cause of blindness, leg amputations, and chronic renal disease. Hyperglycemia inT2DM becomes manifest once insulin secretion is no longer adequate for the metabolic demands of the individual. The approach to glycemic management of the disease is increasingly based on understanding the underlying pathophysiology. Efforts to maintain and preserve β-cell function during the earlier phases of the disease may have important implications in prevention of subsequent complications of T2DM. Finally, the approach to glycemic management of the disease should be individualized by considering the psycho-socio-economic condition of each patient, and glycemic targets should reflect presence of comorbid conditions, *age* of the patient, the *stage* of their disease in terms of duration, presence of macro- and micro-vascular complications, and propensity for severe hypoglycemia.

Keywords: β-cell number, disposition index, glycemic target range, insulin resistance

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Introduction

A glance at the Centers for Disease Control and Prevention website (http://www.cdc.gov/media/pressrel/2010/r101022.html) stating that the number of persons in the United States with type 2 diabetes mellitus (T2DM) will double or triple by 2050, or at the diabetes map of the world by International Diabetes Federation (http://www.diabetesatlas.org/) convincingly shows the unfortunate and pandemic nature of T2DM. The increase in incidence of T2DM is attributable to changes in lifestyle, diet and obesity, but other causes such as the roles of pollutants and environmental toxins remain to be further defined.[1] In a survey of the 10 leading risk factors for death among countries stratified according to their income levels, high blood glucose and overweight or obesity ranked 3rd and 5th, respectively, and high blood glucose ranked 5th or 6th in low-, middle-, and high-income countries, repsectively.[2] T2DM is the leading cause of blindness, non-traumatic lower limb amputation, and chronic kidney disease requiring dialysis or renal replacement. In addition, the major cause of early mortality in patients with T2DM is attributable to progressive atherosclerosis and cardiovascular disease (CVD).[3,4] T2DM is a major contributor to the very large rise in the rate of non-communicable diseases affecting developed as well as developing nations.[5] The current and future burden of T2DM on health status, life span of individuals, and personal and societal cost cannot be over-stated.

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Pathophysiology and natural history of T2DM

T2DM is a chronic, progressive metabolic disease defined by the presence of hyperglycemia. The disease is incompletely understood and represents a complex metabolic condition. It is characterized by hyperglycemia, insulin resistance, decreased β-cell numbers and maximal secretory function, increased glucagon secretion and hepatic glucose production, hypertension, abnormalities in adipocyte and lipid metabolism, decreased incretin effect, rapid gastric emptying, increased appetite, obesity, systemic inflammation, elevated cytokines, hypercoagulation, and endothelial cell dysfunction.[6–9]

Underlying the abnormal glucose homeostasis in T2DM is resistance to some actions of insulin (importantly stimulation of glucose transport and suppression of hepatic glucose release), inadequate secretion of insulin to match metabolic needs, and increased production of glucose by the liver. A schematic of the natural history of T2DM is depicted in Figure 1A. Insulin resistance (the inverse of insulin-sensitivity) is commonly increased in the "pre-diabetes" phase, but normal glucose levels are maintained as long as β-cells can secrete higher amounts of insulin.[10] However, although during the pre-diabetes phase insulin secretion is stimulated, the levels are less than what is needed; this reflects decreases in responsiveness of β-cells to glucose and in maximal β-cell secretory capacity. There is also decreased responsiveness of the liver to insulin (to suppress glucose production by gluconeogenesis and glucose release by glycogenolysis), and increased resistance of muscle to insulin (to stimulate glucose uptake); the resistance to actions of insulin in peripheral tissues, including adipocytes, reflect post-receptor defects in the insulin-signaling pathway.

Of clinical significance is the decrease in the number of β-cells in islets of patients with T2DM (Figure 1B), and a decrease in

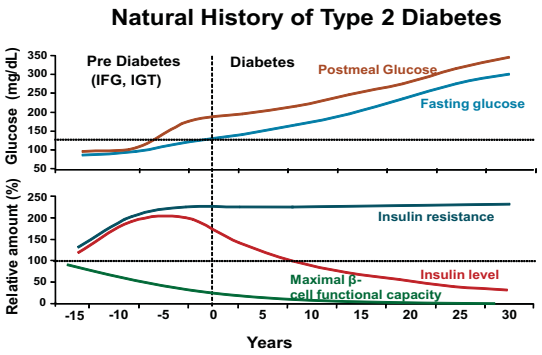

Figure 1A.

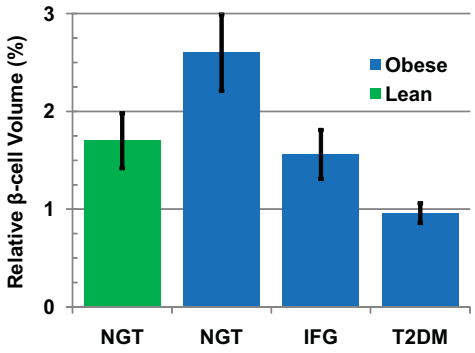

Figure 1B.

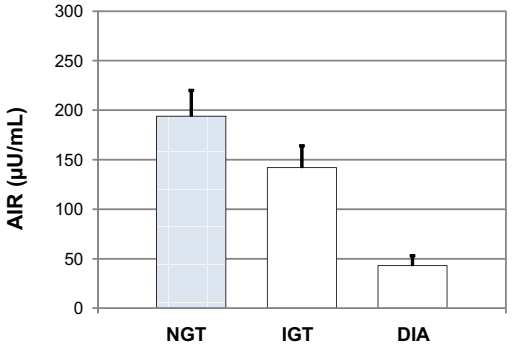

Figure 1C.

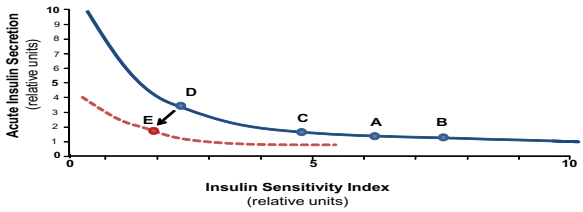

Figure 1D.

Figure 1. Natural history of T2DM: central role of β-cell function. A) An idealized drawing of the natural history of T2DM. Adapted from Kendall DM, et al.[10] The vertical dotted line at year 0 depicts the time of diagnosis. Top: Post-meal glucose rises before time 0 (Pre-diabetes), and both post-meal and fasting glucose rise over time after diagnosis (Diabetes). Bottom: Insulin resistance rises and may remain relatively constant over time, whereas the high insulin levels prior to diagnosis (which is not adequate for the level of pre- and post-prandial glycemia) slowly fall with progression of the disease. β-cell function (maximal secretory capacity) deteriorates over time and is ~50% of normal (or less) at diagnosis. **B)** Relative β-cell volume. Data are from Butler et al.[11] β-cell volume (as an indicator of β-cell mass) is increased in obese individuals with normal glucose tolerance (NGT), perhaps as an adaptation to greater insulin requirement; mean ± SE. Obese individuals with impaired fasting glucose (IFG) have a decrease in β-cell volume, which is further decreased in T2DM. **C)** β-cell function in T2DM. Redrawn from Weyer et al.[13] The acute insulin response to a bolus of intravenous glucose is from a longitudinal study of a cohort of Pima Indians who developed T2DM over time (NGT = normal glucose tolerance; IGT = impaired glucose tolerance; DIA = T2DM). In comparison with Panel B, β-cell function is decreased more than relative β-cell volume. **D)** Insulin secretion as a function of insulin sensitivity. The solid line (also identified as the disposition index) depicts the values derived from a population of normal individuals. Of note, the parameters vary several-fold on either axis. Inheritance appears to play a dominant role in the degree of insulin secretion and insulin sensitivity, while differences in body fat content also have an important role in the variability in insulin sensitivity. In addition to the distribution shown in populations, adaptive changes can also occur in individuals. For example, a person at point A who develops an increase in insulin sensitivity (perhaps due to exercise and loss of fat mass) and moves to point B, or a person who develops a decrease in insulin sensitivity and moves to point C can maintain euglycemia as long as they remain on the normal distribution curve. However, normal persons with low insulin sensitivity and high insulin secretion may be limited in their adaptive response, and a further decrease in their sensitivity to insulin (as seen during the last trimester of a normal pregnancy, following gain in body fat, or use of excessive glucocorticoids) if not matched by an increase in insulin secretion may lead to hyperglycemia. Finally, a person at point D who develops a decrease in insulin sensitivity plus a decrease in insulin secretion (and moves to point E) is prone to T2DM or has developed the disease (dotted line).

maximal insulin secretory capacity per β-cell.[11,12] Examination of Figure 1B based on autopsy results, and taking into account that means ± SE are shown, one can readily see that there is tremendous variation in the number of β-cells among normal individuals. Of note, relative β-cell volume varies greatly (5 to 7-fold) among normal individuals and in each of the categories shown in the figure; the large variation in relative β-cell volume is most likely an inherited trait that may be modified by intrauterine milieu during gestation.[11,12] One can also see that there are increased numbers of β-cells in obese persons (perhaps an adaptive response), and there are decreasing numbers of β-cells in individuals with pre-diabetes and T2DM. Based on longitudinal studies on Pima Indians,[13] in addition to other studies,[14] there is at least a 50% loss of maximal β-cell function at the time of diagnosis of T2DM[6,15] (Figure 1C). The β-cell failure, which is also age-related, is mediated by a combination of genetic factors, exposure to elevated levels of glucose and free fatty acids in blood (gluco- and lipo-toxicity, respectively), possibly deposition of amyloid fibrils in islets, and increased demand to secret more insulin in response to ambient hyperglycemia. It is noteworthy that the bulk of the currently described genetic abnormalities associated with T2DM are related to β-cell function.[16,17] The critical role of β-cell failure in the development of T2DM has significant implications in the management of the disease.

Examination of Figure 1D is also of great interest. The figure shows the relationship between insulin secretion and insulin sensitivity in normal euglycemic individuals. Critical to our understanding is the fact that there is great variation in insulin secretion

as well as in insulin sensitivity among normal individuals. The underlying causes for this vast variation are unclear; most of the variation is not explained by adiposity and probably reflects genetic or epigenetic factors. Although the figure depicts the relationship among different normal individuals, each person has the ability of moving left or right on the x-axis (insulin sensitivity). For example, a person who gains weight may have a decrease in his or her insulin sensitivity, but will continue to have normal blood glucose levels as long as insulin secretion increases. Hence, T2DM represents a condition where insulin secretion is much less than what is needed, given the degree of insulin resistance in the individual.

Diagnosis and evaluation

The diagnosis of T2DM, as currently outlined by the American Diabetes Association (ADA), is based on an A1C $\geq$ 6.5%, or fasting plasma glucose level $\geq$ 126 mg/dL (7.0 mmol/L), or 2-h plasma glucose $\geq$ 200 mg/dL (11.1 mmol/L) during an oral glucose tolerance test, or the presence of classical symptoms of hyperglycemia and a random plasma glucose $\geq$ 200 mg/dL.[18] Diagnostic measures recommended by the American Association of Clinical Endocrinologists (AACE) considers an A1C $\geq$ 6.5% to be an optional criterion.[19]

Patients with newly-recognized T2DM often have had a slow progression of the disease for a few to many years prior to diagnosis. Evaluation of patients with T2DM should include past history of CVD, and family history of T2DM and CVD. Blood pressure (BP), BMI, physical activity, diet, comorbidities, renal function, presence of microalbuminuria, retinopathy, or neuropathy, serum cholesterol LDL, HDL, and TG, and smoking status should be evaluated.

The goal of glycemic control

The overall aim of glycemic management is to prevent long-term macrovascular and microvascular complications of T2DM while avoiding (or at least greatly minimizing) episodes of severe hypoglycemia (defined as episodes requiring third-party assistance), and enabling a good quality of life. Evidence from large randomized trials both in type 1 diabetes and newly-recognized[20–22] or established T2DM[23–27] show that control of glycemia delays onset and slows progression of microvascular complications of diabetes, including nephropathy, retinopathy, and neuropathy. On the other hand, recent trials that have been conducted in older patients with established T2DM and a history of CVD or one or more risk factors for CVD have found no reduction in total mortality or CVD-related mortality from intensive lowering of glucose to normal or near-normal glycemic levels compared to standard glycemic control. They also reported higher rates of severe hypoglycemia and weight gain with intensive treatment.[24,25,28,29] However, long-term follow-up of patients with newly-diagnosed T2DM whose hyperglycemia had previously been treated intensively resulted in reduced CVD events.[30] Clearly, the benefits derived from intensive glycemic control must be weighed against risks for each individual patient.

While this article is specifically focused on glycemic management of T2DM, it is critical to appreciate that T2DM is a complex metabolic condition, and that glycemic control is only one facet of the proper management of T2DM. Hence, a multifactorial approach aimed at control of all known risk factors for development of CVD and microvascular disease as well as life-style changes is essential.[31,32] Moreover, given the multiple abnormalities that underlie the hyperglycemia of T2DM, simultaneous control of the different pathways might be advantageous.

Considerations for setting glycemic targets

An important first step in glycemic management is setting an appropriate glycemic target for each individual patient with T2DM. The current guidelines specify general A1C targets of < 7.0% or < 6.5%.[18,33] However, the critical role of patient-specific psychological, social, and economic conditions and the patient's capacity for self-management in choosing an appropriate glycemic target cannot be overemphasized.[34] Issues to be considered include safety of the recommended strategy, especially in those with a higher risk for severe hypoglycemia. More intensive treatment usually means use of a higher number and dosages of medications resulting in increasing adverse effects and cost. The psychological and cognitive status of the patient constitutes important determinants of whether the treatment plan will be successful.[34,35] Hence, evaluation of the psychological state and a mini-mental exam are useful. The financial cost of the prescribed treatment plan needs to be considered. Finally, the ultimate goal of enhancing the patient's quality of life must not be forgotten, and glycemic targets should be adapted to changes in the patient's health and living conditions.

The presence of other severe comorbid conditions that are debilitating and could interfere with implementation of the management strategy should be targeted to higher A1C levels (Table 1). Here the goal is prevention of large glycosuria, water and electrolyte loss, infections, and development of non-ketotic hyperosmolar coma. In general, the higher the age of the patient and the longer the duration of the disease, the more significantly established is the atherosclerotic process and microvascular derangements, which portend less benefit from intensive glycemic treatment. Intensive treatment of glycemia in patients with T2DM, especially with insulin or sulfonylureas, can result in episodes of severe hypoglycemia. Older patients with low cognitive function are prone to develop severe hypoglycemia, and dementia has been reported with episodes of severe hypoglycemia.[36,37] Severe hypoglycemia in patients with T2DM and CVD may lead to myocardial ischemia, and may increase the risk of myocardial infarction, cardiac arrhythmias, or sudden death.[38,39] The intensity of glucose control should be immediately relaxed by an average of ~45–60 mg/dL (~1.5% to 2.0% HbA1C)[40] for at least several weeks following a severe hypoglycemic episode. Further relaxation of glycemic goals for more prolonged periods should be considered following 2 or more episodes. The glycemia target in patients with "hypoglycemia unawareness" should be markedly relaxed for a very prolonged period, awaiting the potential reversal of the condition.

Figure 2 summarizes the influence of clinical features on selection of an A1C target for a specific patient from a spectrum of A1C goals.[34] In general, the evidence suggests that in younger patients with recently-recognized T2DM and little (or no) complications, near-normal glycemic targets aimed at prevention of complications over many years of life can be suggested. In contrast, in older individuals with established T2DM and evidence of CVD (or multiple CVD risk factors), somewhat higher targets may be more appropriate.

The glycemic goal for each patient should be individualized and take into consideration their psycho-socio-economic condition and a spectrum of A1C values rather than a set A1C number.[34] Individualization of the target range according to the presence of

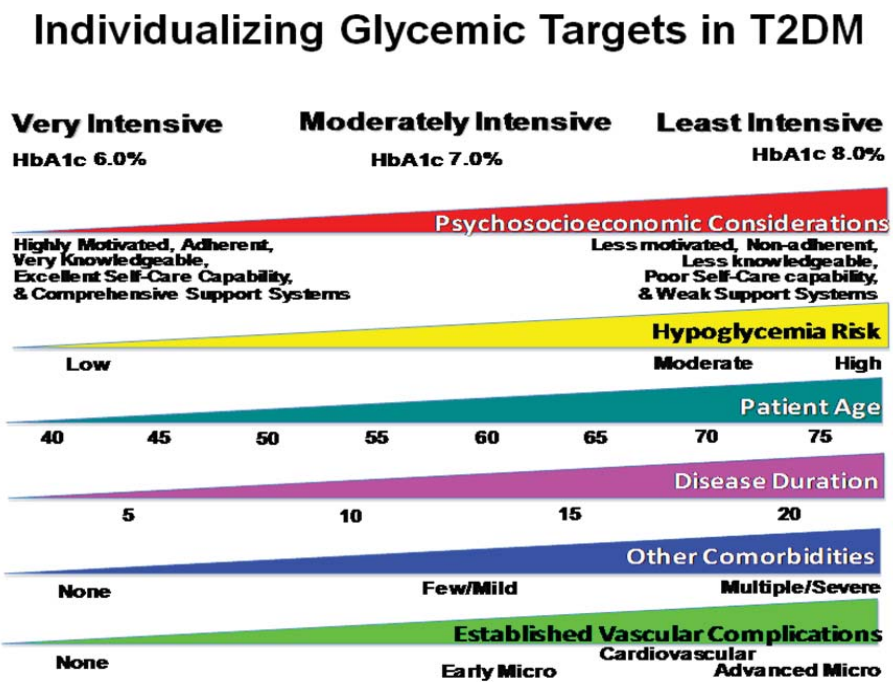

Figure 2. Suggested glycemic treatment goals in patients with T2DM.[§]
The figure depicts glycemic goals and treatment intensities with increasing severity or magnitude of clinical parameters, as well as with increasing limitations in the psycho-socio-economic context. The increasing height of the triangles reflects increases in the considered parameter. The positions of the triangles in the figure are not meant to represent their relative importance in setting glycemic targets.
[§] While there is a strong positive correlation between HbA1C and mean blood glucose levels in populations, there is also significant individual variation as well as variation in populations (for a variety of medical, non-medical, and unknown reasons) both between glucose levels at a given HbA1C and HbA1C values at a given average blood glucose level.[38] The figure is adapted from Ismail-Beigi et al.[34]

severe comorbid conditions, *age* of the patient, the *stage* of their disease both in terms of *duration* and *presence of macro- and micro-vascular complications*, and propensity for *severe hypoglycemia* should be considered (Figure 2).[34]

General glycemic treatment considerations

Ideal strategies for effective long-term glycemic control place the patient at the center of the decision-making process. Time devoted to education and dialogue is required to achieve goals. The important roles that nurses, nutritionists, certified diabetes educators, and other staff play in this process cannot be overemphasized. A balanced diet rich in fiber, with control of total calories and free carbohydrates should be advocated.[32,41] Exercise has an independent and additive effect to a proper diet and weight loss program on glycemic control.[42–44] Smoking cessation should be emphasized. Much success, at lower cost and greater satisfaction, has been reported with the use of telecommunication and computer-based data transfer systems.[45,46]

The rapidity of reaching the glycemic target range needs consideration. Although there are no set rules, several parameters appear important, including the fact that the disease is chronic and that adaptive changes to the hyperglycemic state have taken place; the level of hyperglycemia, the capabilities and wishes of the patient based on knowledge and understanding, the degree of acceptance for frequent self glucose-monitoring, and their ability to prevent severe hypoglycemic events constitute other important considerations. It is often prudent to achieve the A1C target in stages over a few to several months.

Medical approaches

Different classes of pharmaceutical agents available for glycemic management of T2DM, the expected reductions in A1C, their mechanism of action, effects, and their potential advantages and disadvantages are listed in Table 2.[47–61] The list has greatly expanded in the past two decades. Because the various medications are listed in multiple publications and reviews, they will only be briefly reviewed here.[62–64] Insulin and its analogs, used either singly or in combination with other medications, continue to be the strongest agent in reducing glycemia. However, insulin use is also associated with a high risk for severe hypoglycemia. In early to mid-stages of T2DM, addition of bedtime long-acting insulin (starting with 10–15 units and titrating up by 2–3 units every 4–7 days) can reduce A1C by 1.5%–2.0%, or more.[47,50,65–67] Use of short-acting and long-acting analogs is more popular than human regular insulin or NPH, but very strong evidence in their favor is lacking. Metformin is the cornerstone of treatment of T2DM; it is generally well tolerated, has few side effects, and rarely causes severe hypoglycemia.[18,33,53] Sulfonylurias constitute a popular class of oral medications; their efficacy becomes limited over years, and their use, especially in patients with compromised renal function, is associated with severe hypoglycemia. Glinides have a short duration of action (hours) and are most effective when used pre-prandially. GLP-1 agonists (given by injection) and oral DPP-4 inhibitors are newer insulin-providing agents; they are unique in

Table 1. Patient-specific clinical features considered in defining glycemic targets.

1)	Severe comorbid conditions
2)	Age
3)	Duration of T2DM
4)	Presence of CVD
5)	Presence of microvascular complications
6)	History of severe hypoglycemia

Table 2. Pharmacological agents for treatment of type 2 diabetes.

Class	Agents	Expected reduction in A1C (%)	Mechanism	Effects	Advantages (A) Disadvantages (D)
Insulin-providing					
Insulin	Short-acting: Human insulin, Aspart, Humalog, Glulisine Long-acting: NPH, Glargine, Detemir Mixed insulin preparations	1.0–2.5	Activate insulin receptors	↑ glucose disposal ↓ gluconeogenesis ↓ lipolysis, proteolysis, and ketogenesis	(A) Effective in all patients; large effect. (D) Severe hypoglycemia; injection; cost, weight gain.
Sulfonylurea	Glyburide, Glipizide, Glimepiride	1.0–2.0	Close K_{ATP} channels	↑ insulin secretion, mostly in response to an increase in plasma glucose	(A) Oral agents; not expensive. (D) Severe hypoglycemia; durability.
Glinide	Repaglinide, Nateglinide	0.5–1.0	Close K_{ATP} channels	↑ insulin secretion, mostly in response to an increase in plasma glucose, short duration of action	(A) Oral agents; not expensive; short duration of action; hepatic clearance. (D) Efficacy; severe hypoglycemia.
GLP-1 agonist	Exenetide, Liraglutide	0.5–1.5	Activate GLP-1 receptors	↑ insulin secretion ↓ glucagon secretion ↑ satiety, delays gastric emptying	(A) Rare severe hypoglycemia; weight loss. (D) Injections; cost; nausea and vomiting; ? pancreatitis; ? c-cell tumors of thyroid; ? long-term safety.
DPP-4 inhibitor	Sitagliptin, Saxagliptin, Vildagliptin, others being developed	0.5–0.8	Inhibit DPP-4 enzyme	↑ endogenous GLP-1, ↑ insulin secretion, ↓ glucagon secretion	(A) Oral agents; rare severe hypoglycemia. (D) Less efficacy; cost; ? pancreatitis; ? long-term safety.
Insulin - nsitizing					
Biguanide	Metformin	1.0–2.0	Activate AMPK	↓ hepatic glucose production	(A) Oral agent; rare hypoglycemia; well-tolerated; safe; inexpensive; durability. (D) GI intolerance.
Thiazolidinedione	Pioglitazone	0.5–1.4	Activate PPAR-γ nuclear receptors	↑ insulin sensitivity in muscle and liver	(A) Oral agent, ? reduced CVD. (D) Side effects including edema, heart failure, weight gain, fractures; ? bladder cancer
Other					
Amylin analogue	Pramlintide	0.5–1.0	Activate amylin receptor	↓ glucagon secretion ↑ satiety, delays gastric emptying	(A) Weight loss. (D) Injection; nausea and vomiting; cost.
α-glucosidase inhibitor	Acarbose, Miglitol	0.5–0.9	Inhibit α-glucosidase in the small intestine	↓ carbohydrate absorption	(A) Oral agents. (D) Gas production.
Bile acid sequestrant	Colesevelam	~0.5	Bind bile acids	Not known	(A) Lowers cholesterol. (D) GI tolerance; efficacy; cost.
D2-dopamine agonist	Boromocriptine (rapid release)	~0.5	Activate D2-dopaminergic receptors	Alters hypothalamic control of insulin sensitivity in peripheral tissues	(A) Oral agent; long-acting available (D) efficacy; some GI side effects; cost

their suppression of glucagon secretion. Control of appetite with weight loss of a few to several kilograms can be associated with the use of GLP-1 agonists. The long-term safety of these newer agents is under study. Pioglitazone acts to increase insulin sensitivity; untoward side effects include weight gain, edema, heart failure, and risk of fractures, especially in women.[60] Additional less frequently used agents are listed under "Other" in Table 2.

Given the multiple pathogenic mechanisms of T2DM, use of multiple agents with complementary modes of action to control glycemia, and if possible, preserve β-cell function before it reaches critically low levels can be considered; however, convincing evidence for beneficial effects of this approach is lacking.[68,69] The recommended choice of combination of agents depends on the stage of the disease and the degree of β-cell dysfunction. Effective combinations include metformin plus long-acting insulin at bedtime, and metformin plus a DPP-4 inhibitor, a GLP-1 agonist, a glinide, or pioglitazone. Metformin plus a sulfonylurea is a less desirable, but commonly used combination. Long-acting insulin plus a glinide can also be considered. Insulin is often added much later than medically indicated.[47,53,67]

Surgical approaches for glycemic control

Bariatric surgery, and the resultant large weight loss, has proven to be a highly effective mode of treatment for T2DM in very obese individuals.[70,71] Different gastric bypass and gastric limiting procedures differ in their efficacy for treatment of diabetes, and the mechanisms underlying their effect on glucose homeostasis is under investigation. In general, procedures that greatly limit the absorptive surface are the most efficacious but also have the highest rates of complications.[71] The potential long-term untoward effects of these procedures are being determined.

Unknowns and areas to be explored

The underlying cause(s) of accelerated CVD in T2DM, and the role of glycemic control in this process remain to be fully determined. A better understanding of the genetic and environmental factors underlying the large variation in insulin resistance and β-cell number and function in normal persons is critical to strategies to prevent and more effectively treat T2DM. Given the millions of people who will be newly-diagnosed with T2DM in the next two decades, it is critical that evidence favoring treatment modalities that help preserve β-cell function be generated.[69] While there is general agreement on the first-line use of metformin, evidence is lacking to inform the superiority of the additional agents to be employed in conjunction with metformin. More information is necessary on setting of appropriate glycemic targets and how best to individualize therapy. Finally, assessment of long-term safety of GLP1 agonists and DPP-4 inhibitors should be provided.

Conclusion

T2DM is an incompletely understood multifactorial disease with insulin resistance and decreased β-cell function playing dominant roles in its genesis. Hyperglycemia in T2DM becomes manifest once insulin secretion by β-cells is no longer adequate for the metabolic demands. The approach to glycemic management of the disease is evolving and increasingly based on understanding the underlying pathophysiological disturbances. Efforts to maintain and preserve β-cell function during the earlier phases of the disease may have implications in prevention of subsequent complications of T2DM. Finally, the approach to glycemic management of the disease should be individualized by considering the psycho-socio-economic condition of each patient, and glycemic targets should reflect presence of severe comorbid conditions, ***age*** of the patient, the ***stage*** of their disease both in terms of duration and presence of macro- and micro-vascular complications, and propensity for severe hypoglycemia.

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