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Management of type 2 diabetes: evolving strategies for the treatment of patients with type 2 diabetes

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ABSTRACT

The prevalence of type 2 diabetes continues to increase at an alarming rate around the world, with even more people being affected by prediabetes. Although the pathogenesis and long-term complications of type 2 diabetes are fairly well known, its treatment has remained challenging, with only half of the patients achieving the recommended hemoglobin A_{1c} target. This narrative review explores the pathogenetic rationale for the treatment of type 2 diabetes, with the view of fostering better understanding of the evolving treatment modalities. The diagnostic criteria including the role of hemoglobin A_{1c} in the diagnosis of diabetes are discussed. Due attention is given to the different therapeutic maneuvers and their utility in the management of the diabetic patient. The evidence supporting the role of exercise, medical nutrition therapy, glucose monitoring, and antiobesity measures including pharmacotherapy and bariatric surgery is discussed. The controversial subject of optimum glycemic control in hospitalized and ambulatory patients is discussed in detail. An update of the available pharmacologic options for the management of type 2 diabetes is provided with particular emphasis on newer and emerging modalities. Special attention has been given to the initiation of insulin therapy in patients with type 2 diabetes, with explanation of the pathophysiologic basis for insulin therapy in the ambulatory diabetic patient. A review of the evidence supporting the efficacy of the different preventive measures is also provided.

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1. Introduction

Type 2 diabetes mellitus (T2DM) is a heterogeneous disorder, characterized by defects in insulin secretion and insulin sensitivity [1,2]. Insulin resistance by itself will not result in T2DM unless β -cell secretion of insulin is decreased. Based on the Centers for Disease Control and Prevention National Diabetes Fact Sheet in 2007 [3], there were 23.6 million Americans with diabetes, of whom 90% to 95% have T2DM; 17.9 million of type 2 diabetic patients are diagnosed while 5.7

million are undiagnosed. Diabetes statistics suggest the prevalence rate of prediabetes is 25.9% (impaired fasting glucose and impaired glucose tolerance [IGT]) with 57 million people being affected. The total direct and indirect cost of diabetes in 2007 was 174 billion dollars [3]. The prevalence of obesity and diabetes appears to run parallel to each other, as indicated by the fact that epidemics of obesity and diabetes are parallel in various regions of the United States. For example, the prevalence of obesity has increased from 10% to 14% in 1991 to 20% to 24% in 2001. Similarly, the prevalence

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of T2DM has increased from 4% to 6% in 1991 to 8% to 10% in 2001 [4].

The nonmodifiable causes of diabetes include age, ethnicity, and genetics, whereas the modifiable causes include weight/body mass index, central adiposity, and sedentary lifestyle. The impact of diabetes on US mortality is significant—72 507 deaths in 2006, the seventh leading cause of death, and an additional 233 269 deaths linked to diabetes [3]. Diabetes mellitus is the leading cause of new blindness and chronic renal disease, leading to dialysis and nontraumatic amputation. The severity of carbohydrate intolerance correlates with cardiovascular disease and mortality. Mortality rate in persons with normal glucose tolerance is about 1.2 per 1000 patients, whereas in IGT, mortality is about 2.8/1000 patients, and in T2DM, is about 4 times that of normal glucose-tolerant subjects [5].

Table 1 depicts the 2010 American Diabetes Association (ADA) criteria for diagnosis of glucose tolerance, where fasting blood glucose of less than 100 mg/dL and 2-hour postprandial blood glucose of less than 140 mg/dL are considered within normal range [6]. This table also shows that there are 3 ways to diagnose diabetes: (a) fasting blood glucose of 126 mg/dL or greater; (b) 2-hour postprandial of 200 mg/dL or greater; or (c) random blood glucose of 200 mg/dL or greater with complaint of polyuria, polydipsia, and unexplained weight loss. The diagnosis of diabetes should be confirmed with one additional test to rule out laboratory error, unless the diagnosis is clear on clinical grounds, such as in a patient with classic symptoms of hyperglycemia or hyperglycemic crisis. The diagnosis of IGT includes a 2-hour postprandial of 140 to 199 mg/dL after oral glucose tolerance test (OGTT), while impaired fasting consists of a glucose value of 100 to 125 mg/dL. It is clear that for a diagnosis of IGT, an OGTT should be performed, but in general, a fasting blood glucose greater than 100 mg/dL should alert providers to confirm IGT by an OGTT.

Table 1 – Criteria for the diagnosis of diabetes

1. $A_{1c} \geq 6.5\%$. The test should be performed in a laboratory using a method that is NGSP certified and standardized to the DCCT assay.^a
OR
2. FPG ≥ 126 mg/dL (7.0 mmol/L). Fasting is defined as no energy intake for at least 8 h.^a
OR
3. Two-hour plasma glucose ≥ 200 mg/dL (11.1 mmol/L) during an OGTT. The test should be performed as described by the World Health Organization, using a glucose load containing the equivalent of 75 g anhydrous glucose dissolved in water.^a
OR
4. In a patient with classic symptoms of hyperglycemia or hyperglycemic crisis, a random plasma glucose ≥ 200 mg/dL (11.1 mmol/L).
5. Categories of increased risk for diabetes^b
FPG 100–25 mg/dL (5.6–6.9 mmol/L) [IFG]
Two-hour plasma glucose on the 75-g OGTT 140–199 mg/dL (7.8–11.0 mmol/L) [IGT] A_{1c} 5.7%–6.4%

NGSP indicates National Glycohemoglobin Standardization Program; FPG, fasting plasma glucose. Adapted from reference [6].

^a In the absence of unequivocal hyperglycemia, criteria 1 to 3 should be confirmed by repeat testing.

^b For all 3 tests, risk is continuous, extending below the lower limit of the range and becoming disproportionately greater at higher ends of the range.

A hemoglobin A_{1c} level of greater than 6.5 % was recommended in June 2009 by the International Expert Committee on the role of hemoglobin A_{1c} assay in the diagnosis of diabetes as the cut-point for the diagnosis of diabetes [7]. The committee cautioned that this value should not be taken as an absolute dividing line between normoglycemia and diabetes but observed that a hemoglobin A_{1c} level of 6.5% had the requisite sensitivity and specificity to identify subjects at risk for developing diabetic retinopathy, and therefore should be used as a diagnostic cut-point. The expert committee recommended that clinicians should continue to use the previously recommended approaches to diagnose diabetes based on glucose measurements where it is not feasible to use hemoglobin A_{1c} . It is also reasonable to consider a hemoglobin A_{1c} range of 5.7% to 6.4% as identifying individuals with high risk for future diabetes and to whom the term *prediabetes* may be applied if desired [6]. As is the case for individuals found to have IFG and IGT, individuals with a hemoglobin A_{1c} level of 5.7% to 6.4% should be informed of their increased risk for diabetes as well as for cardiovascular disease and counseled about effective strategies to lower their risks. The diagnostic test should be performed using a method that is certified by the National Glycohemoglobin Standardization Program and standardized to the Diabetes Control and Complications Trial (DCCT) assay. Point-of-care hemoglobin A_{1c} assays are not sufficiently accurate at this time to use for diagnostic purposes [6].

It should be noted that clinical conditions that affect red cell turnover, such as hemolytic anemia, chronic malaria, major blood loss, or blood transfusions, are likely to produce false hemoglobin A_{1c} results. Furthermore, hemoglobinopathies such as HbS, HbC, HbF, and HbE may interfere with some assay methods, thus giving spurious results. Blood glucose values should be used in these circumstances. In addition, hemoglobin A_{1c} values have been shown to vary among ethnic groups with IGT after adjusting for other factors. Therefore, caution should be used when comparing these values across ethnic groups [8].

2. Pathogenesis of T2DM

Fig. 1 depicts the pathogenesis of T2DM. Type 2 diabetes mellitus has a progressive nature, preceded with a period of insulin resistance and IGT. Endogenous insulin secretion in IGT may be increased to maintain fasting blood glucose within normal range; however, during this time, the 2-hour postprandial blood glucose is elevated to a level of 140 to 199 mg/dL as endogenous insulin secretion is decreased and ultimately leads to T2DM [9]. The conversion from IGT to T2DM may take from 9 to 12 years unless there are lifestyle modifications (LSMs) or other therapies that may reduce this risk [9]. Type 2 diabetes mellitus usually develops in subjects with β -cell dysfunction in the presence of insulin resistance at the level of muscle, fat and liver [1]. The contributing factors to β -cell dysfunction in T2DM are gluco- and lipotoxicity [2]. Fig. 2 [11] depicts the triad of metabolic syndrome, insulin resistance, and diabetes mellitus, where inflammation, stress, and endothelial dysfunction are the common denominators in these 3 conditions with a final outcome of micro-, macro-, and cerebrovascular events.

Insulin Deficiency Due to β -Cell Failure

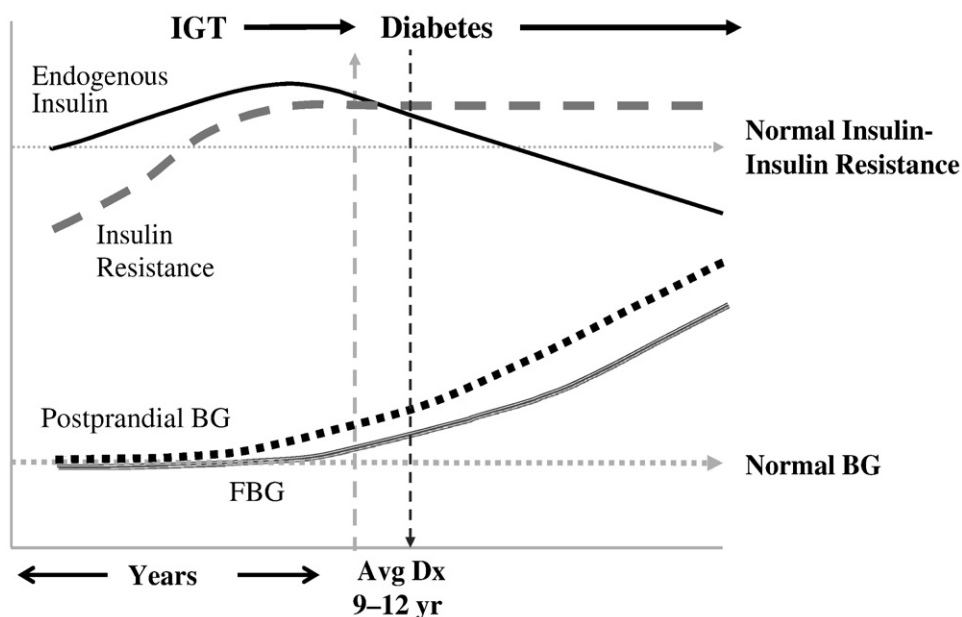


Fig. 1 – Progressive nature of type 2 diabetes. Adapted from reference [9].

In addition to defective insulin action and secretion, patients with T2DM also exhibit nonsuppressible glucagon secretion after a meal [10]. Glucagon-like peptide 1 (GLP-1) is an incretin with 5 major physiologic roles: (a) it is secreted from L cells of the intestine upon food ingestion; (b) it regulates gastric emptying; (c) it enhances glucose-dependent

insulin secretion; (d) it decreases glucagon secretion postprandially; and (e) it promotes satiety and reduction in appetite with noticeable weight loss [12]. The difference between oral glucose-derived insulin secretion and intravenous (IV)-derived insulin secretion is the incretin effect, which is increased with oral glucose as compared to IV glucose.

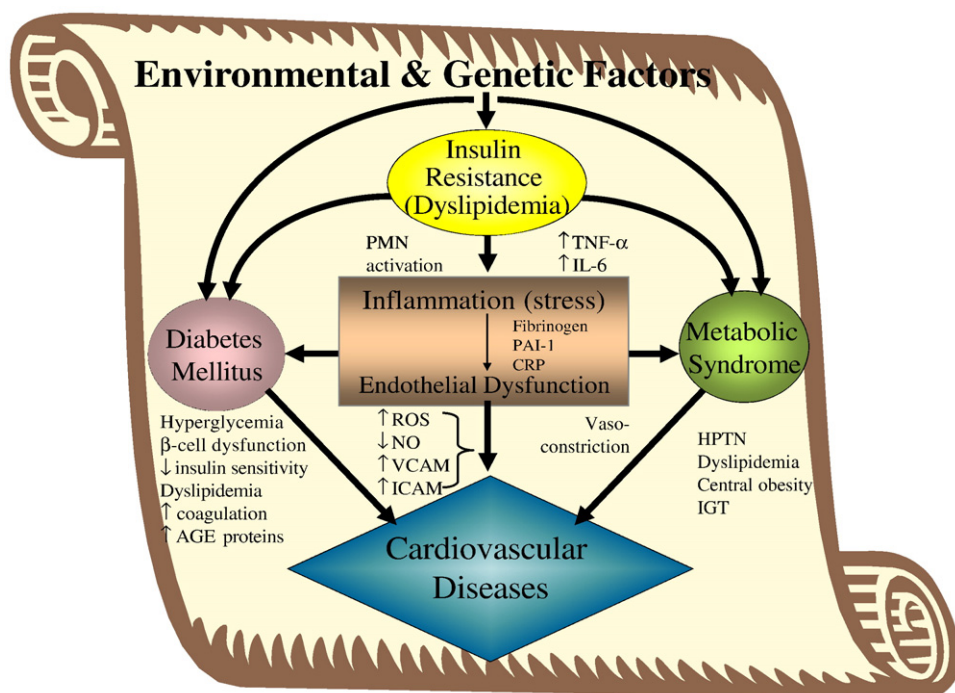


Fig. 2 – Aberrant pathways in the development of cardiovascular disease. Adapted from reference [11].

3. General management of diabetic patients

These consist of:

Education: Education of patients with either prediabetes or diabetes should include the following content areas that are based on assessed needs: (1) disease process; (2) treatment option; (3) nutritional plan; (4) exercise plan; (5) knowledge of diabetes medicine prescribed; (6) blood glucose monitoring; (7) knowledge of acute and chronic complications; (8) psychosocial issues; and (9) individual strategies to promote health [13].

Medical nutrition therapy: Calculation of diet is based on ideal body weight (in pounds) multiplied by 10 to establish a basic kilojoule (kilocalorie) requirement, plus 30% to 100% added for physical activity. The diet should include 50% to 55% carbohydrate, 30% fat (of which no more than 10% should be saturated fatty acids, and 15%–20% protein), as well as fiber. It is important to remember that both portion control in the management of diet and daily exercise play very important roles in maintaining ideal body weight.

Physical activity: Sedentary lifestyle is a powerful but modifiable risk factor for T2DM; therefore, moderate exercise is of utmost benefit in patients with diabetes.

Oral hypoglycemic agents: Table 2 summarizes presently available oral agents and major mechanisms of action. A more detailed treatment of this subject is presented in Section 10.

Insulin: Table 3 depicts presently available insulin preparations in the United States. Patient management will be discussed in Section 10.7.

Table 3 – Insulin preparations

	Onset of action	Peak	Duration of action
Aspart/humalog/glulisine	5 to 15 min	1–2 h	4–6 h
Inhaled insulin	5–15 min	1–2 h	3–6 h
Human regular	30–60 min	2–4 h	6–10 h
Human NPH	1–2 h	4–6 h	10–16 h
Human lente	1–2 h	4–6 h	10–16 h
Human ultralente	2–4 h	Unpredictable	<24 h
Glargine (Lantus)	1–2 h	None	24 h
Detemir (Levemir)	1–2 h	None	24 h

4. Medical nutrition therapy

Medical nutrition therapy, an important component of healthy lifestyle, remains a cornerstone of diabetes prevention and management. Medical nutrition therapy has been shown to accrue sustained reduction in hemoglobin A_{1c} in diabetic patients [13,14] and also improvement in lipid profile and blood pressure in nondiabetic individuals [15,16]. Look AHEAD (Action for Health in Diabetes), an ongoing randomized clinical study investigating the effect of weight loss on cardiovascular end points in people with T2DM, has shown that 1 year of intensive LSM resulted in significant weight loss, as well as improvement in glycemic control and cardiovascular risk factors [17]. The optimum dietary macronutrient composition remains a subject of interest; however, several studies have shown that dietary measures are effective in weight reduction irrespective of the composition (low fat vs low carbohydrate), provided there is adequate energy restriction, reduction in saturated fat to less than 7%, and adequate provision of dietary fiber [18,19]. Although low-fat and low-carbohydrate diets are

Table 2 – Oral antidiabetic agents

Drug class	Brand name	Generic name	Available strengths (mg)	Mechanisms of action
Sulfonylureas	Diabeta	Glyburide	1.25, 2.5, 5	Stimulate pancreatic β cells to increase first-phase insulin secretion May cause hypoglycemia
	Micronase	Glyburide	1.25, 2.5, 5	
	Glynase	Glyburide (micronized)	1.5, 3.0, 4.5, 6.0	
	Glucotrol	Glipizide	5, 10	
	Glucotrol XL	Glipizide	5, 10	
	Amaryl	Glimepiride	1, 2, 4	
Meglitinides	Prandin	Repaglinide	0.5, 1, 2	↓HGO
	Starlix	Nateglinide	60, 120	
Biguanides	Glucophage	Metformin	500, 850, 1,000	Decrease insulin resistance
	Glucophage XR	Metformin	500	
Thiazolidinediones	Actos	Pioglitazone	15, 30, 45	Delay glucose absorption
	Avandia	Rosiglitazone	2, 4, 8	
α -Glucosidase inhibitors	Precose	Acarbose	25, 50, 100	↓HGO Decrease insulin resistance ↑Insulin secretion
	Glyset	Miglitol	5, 50, 100	
Combinations	Glucovance	Glyburide/metformin	1.25/250, 2.5/500, 5.0/500	
	Avandamet	Rosiglitazone/metformin	1/500, 2/500, 4/500	
	Actos + mets	Pioglitazone/metformin	15/500, 15/850	
	Prandimet	Metformin/repaglinide	500/1, 500/2	
DPP IV inhibitors	Januvia	Sitagliptin	25, 50, 100	
	Janumet	Sitagliptin/metformin	50/500, 50/1000	

HGO, hepatic glucose output; DPP IV, dipeptidyl peptidase IV.

both effective in producing weight loss, their effect on lipid profile may differ. Low-carbohydrate diet may yield greater reduction in triglyceride with higher improvement in high-density lipoprotein, but with higher low-density lipoprotein levels in comparison to low-fat diet [20]. Lower consumption of total and saturated fat and processed foods, and higher consumption of fibers, whole grains, fruits, and vegetables have been shown to improve glycemic control in patients with diabetes. In clinical trials, nut consumption increases satiety, have a neutral effect on glucose and insulin, and a beneficial effect on lipid profile [21,22]. Artificial sweeteners may cause diarrhea; otherwise, they are safe when used according to Food and Drug Administration (FDA) recommendation. Although diabetic subjects may have increased oxidative stress, placebo-controlled trials have not demonstrated any clear benefit attributable to antioxidant supplementation [23].

5. Exercise

Sedentary lifestyle is one of the most important risk factors for T2DM. Studies in prediabetic and diabetic subjects have demonstrated benefits of physical activity in the prevention and management of T2DM [17,24,25]. A meta-analysis of 14 trials that investigated the effect of exercise on glycemic control in diabetic patients revealed that engaging in a structured moderate exercise program for about 50 minutes 3 times a week resulted in approximately 0.7% reduction in hemoglobin A_{1c} level in 8 weeks [26]. The mechanisms by which exercise produces positive results in patients with diabetes include improvement in insulin sensitivity and glucose disposal in the skeletal muscle, expression of nitric oxide synthase in the endothelial cells, improvement in obesity, and body fitness. Attention should be paid to the presence of long-term diabetic complications such as coronary or peripheral artery disease, advanced retinopathy, neuropathy, and diabetic foot disease before commencing an exercise program. It should also be noted that poorly controlled patients may develop hyperglycemia during exercise, whereas patients treated with insulin and insulin secretagogues could develop hypoglycemia. Adjustment in the dosage of medications and monitoring of blood glucose during exercise remains a prudent precautionary measure.

To estimate the impact of exercise on energy expenditure, patients should be educated on estimated energy expenditure with various forms of exercise (see Table 4).

Table 4 – How to burn approximately 420 kJ (100 cal)

Activity	Time in minutes
Clean/vacuum/mop floor	25-35
Wash dishes/iron clothes	45-50
Mow lawn (self-propelled mower)	25-30
Mow lawn (manual mower)	12-15
Accessed online from the Healthlink sponsored by the University of Wisconsin.	

6. Antiobesity measures

6.1. Pharmacologic agents

Obesity remains the strongest modifiable risk factor for T2DM. Therefore, measures directed at weight reduction are beneficial in obese diabetic patients. These drugs/surgical procedures should be viewed as adjuncts to LSM. Appetite suppressants offer short-term benefits only but have significant side effects. All currently available over-the-counter and FDA-approved prescription appetite suppressants can elevate heart rate and blood pressure except orlistat. Sibutramine is a serotonin and norepinephrine reuptake inhibitor that induces satiety and prevents a diet-induced decline in the metabolic rate. In the Sibutramine Trial of Obesity Reduction and Maintenance trial, participants lost weight but rapidly regained it on discontinuing the drug where continued use of the drug prevented weight regain [27]. Based on these data, sibutramine and other appetite suppressants should be reserved for people with stable blood pressure who are committed to a lifestyle change program and are aware they will receive adjunct appropriate appetite suppressants only if they show weight reduction of greater than 1 to 2 kg the first 6 weeks of treatment [28]. Monthly weigh-ins should be required for refills.

Orlistat is a lipase inhibitor that reduces fat absorption in the intestine. It is sold over the counter under the name Alli (GlaxoSmithKline, Research Triangle Park, NC). It has also been sold as the prescription drug Xenical (Roche Laboratories Inc., Nutley, NJ). The Xenical in the Prevention of Diabetes in Obese Subjects trial showed better weight loss with orlistat and LSM in patients at risk for T2DM and obesity than with placebo [29]. Orlistat should not be used in patients with cholestasis but can otherwise be used as long-term adjunct to LSM.

Glucagon-like peptide 1 analogs have also been shown to be successful as weight loss agents. A retrospective review of more than 44 000 patients with T2DM treated with exenatide, sitagliptin, or insulin showed that exenatide and sitagliptin were associated with mean weight loss of 3.0 and 1.1 kg, respectively, compared to a weight gain of 0.6 kg in patients treated with insulin [30]. In a smaller randomized placebo-controlled trial, exenatide was associated with 5.3-kg weight loss over 3 years [31]. Furthermore, a recent double-blind, 20-week placebo-controlled trial compared liraglutide treatment once daily to placebo and orlistat 3 times a day orally. Participants treated with liraglutide lost significantly more weight with mean weight loss of up to 7.2 kg compared with 2.8 kg with placebo and 4.1 kg with orlistat treatment. Glucagon-like peptide 1 treatment also reduced the prevalence of prediabetes compared to placebo and orlistat. Nausea and vomiting occurred more often in individuals on liraglutide than in those on placebo [32]. It is worthy of note that incretin mimetics are not approved for weight loss. Although the antiepilepsy drug topiramate has been shown to correct certain components of the metabolic syndrome to improve glycemic control and to aid in weight reduction, it has significant side effects. It is not approved for use as a weight loss aid and is unlikely to be approved for this use [33]. The

cannabinoid receptor blocker remonabant decreases appetite and has been shown to reduce weight and hemoglobin A_{1c} level, improve lipid profile, but affects mood and increases suicidal ideation. Rimonabant is not approved by the FDA for use in the United States or in the European Union because of its side effects including increased heart rate, possible birth defects, and psychiatric problems.

New combination agent compounds in late-stage development include (1) Contrave (Orexigen Therapeutics Inc., La Jolla, CA), which combines long-acting versions of naltrexone and bupropion; (2) Empatic (Orexigen Therapeutics Inc.), which combines long-acting bupropion and long-acting zonisamide; (3) Qnexa (Vivus Inc. Mountain View, CA), which combines phentermine with controlled release topiramate; and (4) an injectable combination of leptin and pramlintide. Peptide YY and melanin-concentrating hormone receptor-1 antagonists are centrally acting agents in early stage development. It is expected that several new drug products for obesity will become available over the next few years [34,35].

6.2. Bariatric surgery

Gastric reduction procedures such as gastric banding and gastric bypass surgery are effective in weight reduction and are associated with significant improvement in glycemic control in patients with T2DM. Patients need to understand that they would still require LSM after surgery. Bariatric surgery should be considered in patients who have body mass index >40 kg/m² or >35 kg/m² and diabetes, in whom diabetic control cannot be achieved with LSM and pharmacotherapy alone [6]. It is recommended that prospective patients engage in 6 months of supervised nutritional management, including education and psychological evaluation before approving the surgery. A meta-analysis of 621 studies, involving more than 135 000 patients, reported that gastric reduction procedures resulted in complete clinical and biochemical resolution of diabetes in 78% of the patients [36]. The degree of glycemic improvement, which was maintained over 2 years, correlated positively with loss of excess body weight. Another study in which 60 patients with recently diagnosed T2DM were randomized to either conventional antidiabetic treatment or surgical weight reduction via laparoscopic gastric banding showed that surgical treatment was associated with remission of diabetes in three quarters of the patients compared to conventional therapy (73% vs 13%) [37]. Furthermore, bariatric surgery has also been shown to reduce all-cause mortality in obese patients by approximately 40% over 7 to 11 years [38,39]; and diabetes- and coronary artery disease-related mortality by 92% and 56%, respectively [38]. A recent prospective randomized study demonstrated that laparoscopic gastric banding was effective in obese adolescents, resulting in loss of more than 50% of excess adiposity in more than 80% of the subjects [40].

However, surgical weight reduction is not without risks [41,42]. Most of the perioperative deaths and morbidity result from anastomotic leaks and catastrophic clotting, but postoperative problems can include bowel obstruction, gallstone disease, stenosis in the gastrointestinal tract, and marginal ulcers. Ulceration is identified in up to 20% of gastric bypass patients within the first 3 months of surgery. Complications

are more common in patients older than 65 years but could be reduced with an experienced surgeon and the use of a facility that performs the procedure frequently. The patients are at risk for long-term fat-soluble vitamin deficiency especially vitamin D and iron deficiency anemia.

7. Monitoring of glycemic control

7.1. Glucose monitoring

The role of self-monitoring of blood glucose (SMBG) in non-insulin-treated patients remains controversial as studies have yielded conflicting results regarding the efficacy of SMBG in achieving optimal glycemic control. However, landmark clinical trials such as the Diabetes Control and Complications Trial, UK Prospective Diabetes Study (UKPDS), and Kumamoto, which demonstrated the effect of diabetes control on the incidence of its long-term complications, also incorporated SMBG to achieve good glycemic control. Thus, these important studies suggest that blood glucose monitoring is an important component of optimum diabetes management. The advantages of SMBG include detection of asymptomatic hypoglycemia, which could be detrimental if it continues without treatment, and identification of hyperglycemic excursions, which may be a risk factor for cardiovascular events. Self-monitoring of blood glucose also enables the patients to learn the effects of food, exercise, and medications on blood glucose levels, which should aid better adherence to therapy and glycemic control. However, glucose monitoring is expensive, and questions have been raised regarding its clinical utility and cost-effectiveness in type 2 diabetic patients who are not treated with insulin. A meta-analysis of SMBG in non-insulin-treated type 2 diabetic patients recorded an improvement in hemoglobin A_{1c} level of about 0.4% [43], which is comparable to a sustained reduction of 0.3% demonstrated in a cohort of 200 diabetic subjects in the Diabetes Outcomes in Veterans Study [44]. However, other studies have not replicated this positive finding, thus bringing to question the clinical utility and efficacy of SMBG [45,46]. Some of these studies are limited by methodological deficiencies such as small sample size and lack of statistical power, lack of training of the patients on how to use the results obtained from blood glucose monitoring, short duration of follow-up, and absence of an adequate control group.

7.2. Hemoglobin A_{1c}

Glycated hemoglobin (hemoglobin A_{1c}), which gives a reliable estimation of the average blood glucose level over 3 months, has been found to correlate tightly with long-term complications in landmark clinical studies [47–49]. Point-of-care testing of hemoglobin A_{1c} level in insulin-treated diabetic patients improved glycemic control by approximately 0.6% in 6 months in a randomized controlled study [50]. The ADA and American Association of Clinical Endocrinologists (AACE) recommend that hemoglobin A_{1c} level testing be done twice a year in well-controlled patients and quarterly in those whose glycemic control is not optimal [6]. Hemoglobin A_{1c} lacks the ability to

Table 5 – Conditions that can falsely increase or decrease HgbA_{1c} values

Falsely low HgbA _{1c}	Falsely high HgbA _{1c}
1. Hemoglobinopathies	1. Hemoglobinopathies
Hgb S	fetal hemoglobin
Hgb D	Hgb Stanleyville II
Hgb GRAZ	Hgb OSU-Christiansborg
Hgb TAKAMATSU	Hgb Raleigh
Hgb G-SZUHU	Hgb D
Hgb ETOBICOKE	Hgb K-Woolwich
Hgb O Padova	2. Carbamylated hemoglobin
methemoglobinemia	3. Anemia
2. Hemolysis	Iron deficiency
3. Medications	Vitamin B ₁₂ deficiency
Dapsone	Folate deficiency
Methylene blue	
Phenacetin	
Benzene derivatives	
Vitamin C excess	
4. Chronic lymphocytic leukemia	
5. Nitrates	
6. Hereditary spherocytosis	
7. Hemodialysis	
8. Venesection	
9. Post blood transfusion	
Hgb indicates hemoglobin.	

detect extreme glycemic excursions; therefore, hemoglobin A_{1c} may be within target in a patient who has recurrent severe hypoglycemia and postprandial hyperglycemia. It may also be falsely low or elevated in different conditions as shown in Table 5. Patients with unexpectedly high or low hemoglobin A_{1c} values may need assessment for abnormal hemoglobins [51]. Both hemoglobin A_{1c} and fructosamine can vary because of other pathologic conditions, but the conditions interfering with the tests are usually not seen in the same patient [52] (Table 6).

Table 7 shows the correlation of hemoglobin A_{1c} with average blood glucose as determined by A_{1c}-Derived Average Glucose trial, which used SMBG and continuous blood glucose monitoring to derive data with correlation of greater than 90% between these 2 measurements [53]. To convert a specific

Table 7 – Correlation of hemoglobin A_{1c} with average blood glucose [47,48]

HgbA _{1c}	Average glucose (mg/dL)
6	126
7	154
8	183
9	212
10	240
11	269
12	298
To calculate estimated average glucose from a specific hemoglobin A _{1c} value, use the following formula: $28.7 \times A_{1c} - 46.7$.	

hemoglobin A_{1c} value to an estimated average glucose, use the following formula: $28.7 \times \text{hemoglobin A}_{1c} \text{ value} - 46.7$ [54].

8. What is optimum glycemic control?

8.1. In hospitalized patients

Patients with diabetes are more likely to be admitted to the hospital for medical and surgical illness than people without diabetes [55,56]. Extensive evidence from observational studies indicate that patients with diabetes have higher rates of hospital complications, longer hospital stay, higher health care resource utilization, and greater hospital mortality than non-diabetic subjects [57–59]. The higher morbidity and mortality in diabetic patients relates in part to the heightened incidence of comorbid conditions including coronary heart disease, heart failure, hypertension, and renal insufficiency [60], as well as the adverse effects of hyperglycemia in clinical outcome [61–65].

8.2. Studies in surgical and medical intensive care units

Extensive observational data have shown a consistent, almost linear relationship between blood glucose levels in hospitalized patients and adverse clinical outcomes in critically ill adult patients with and without diabetes [61–69]. The randomized multicenter Diabetes Mellitus, Insulin Glucose Infusion in Acute Myocardial Infarction study demonstrated that aggressive intervention to control glucose levels significantly reduced morbidity and mortality, regardless of a patient's prior diabetes status [70]. In this study, a total of 620 patients with admission glucose values greater than 198 mg/dL were randomized to receive either conventional diabetes care or IV glucose-insulin-potassium immediately after acute myocardial infarction to maintain levels of blood glucose less than 210 mg/dL followed by intensive subcutaneous insulin therapy for 3 or more months. In this study, mean blood glucose at 24-hour admission to the hospital was 173 mg/dL in the experimental group vs 211 mg/dL in the control group. At discharge, the glucose values were 173 vs 148 mg/dL, respectively. Although the mortality rate in the hospital (control 11% vs insulin glucose infusion 9%) or in 3 months (1% vs 12%) were not significantly different, the values at 1 year were reduced from 26% (control) to 19% (insulin glucose infusion), with a 28% reduction in mortality ($P = .01$).

Table 6 – Conditions that can falsely increase or decrease fructosamine levels [46]

Falsely low fructosamine	Falsely high fructosamine
1. Obesity	1. High glucose diet
2. Hypoproteinemia	2. Hyperbilirubinemia
hypoalbuminemia	3. Low sugar intake
microalbuminemia	4. Hyperuricemia
Peritoneal dialysis	
protein losing enteropathy	
malnutrition	
hemodialysis	
3. Renal failure	
4. Pregnancy	
5. High level of IgA	
6. Hyperlipidemia	
7. High sugar intake	

The Portland Diabetic Project, a prospective, nonrandomized study of 3554 consecutive diabetic patients who underwent coronary artery bypass graft [67], reported that aggressive insulin therapy with IV insulin with blood glucose range of 177 ± 30 mg/dL compared with subcutaneous insulin with blood glucose levels of 213 ± 4 mg/dL resulted in significantly lower mortality rate (2.5% vs 5.3%). Similarly, the rate of deep sternal wound infection, hospital length of stay, and hospitalization costs were significantly reduced in patients treated with IV insulin [71]. Also, Krinsley [72] reported that the implementation of an insulin infusion protocol designed to keep the blood glucose level lower than 140 mg/dL reduced hospital mortality from 20.9% to 14.8% in a prospective study in a medical/surgical intensive care unit (ICU). In the landmark Leuven trial [63], a prospective, randomized study of intensive insulin therapy for patients admitted to a surgical ICU, treated to a target glucose between 4.4 and 6.1 mmol/L (80 and 110 mg/dL), reduced hospital mortality by 34%, sepsis by 46%, acute renal failure requiring hemodialysis by 41%, and need for blood transfusions by 50%. Compared with conventional therapy, there was also less critical illness neuropathy, and shorter durations of mechanical ventilation and ICU stays in these patients [63].

In contrast to these early positive studies, the results of recent randomized controlled studies have raised questions on the safety and efficacy of tight glucose target (80–110 mg/dL) in improving clinical outcomes (reduced hospital complications and mortality) without increasing the risk for severe hypoglycemia [73–76]. The Diabetes Mellitus, Insulin Glucose Infusion in Acute Myocardial Infarction 2 trial [77] included 1253 patients with acute myocardial infarction and a history of diabetes mellitus or admission blood glucose greater than 198 mg/dL reported no difference in mortality among patients randomized to an intensive insulin-glucose infusion protocol or to routine metabolic management according to local practice. In addition, there were no significant differences in morbidity expressed as cases with nonfatal reinfarction, congestive heart failure, and stroke among treatment groups.

The Leuven medical ICU trial failed to replicate the results of the surgical ICU study [78]. In this study, 1200 adult patients considered to need at least 3 days or more of medical ICU care were randomly assigned to receive intensified insulin treatment to achieve a target BG of 80 to 110 mg/dL or to conventional insulin therapy started when blood glucose is greater than 215 to achieve a target blood glucose between 180 and 200 mg/dL. In the intention-to-treat analysis, despite reduction in blood glucose levels, there were no differences in-hospital mortality (40% in the conventional-treatment group vs 37.3% in the intensive-treatment group, $P = .33$). Among 433 patients who stayed in the ICU for less than 3 days, mortality was greater among patients treated with intensive insulin therapy. However, among patients who stayed in the ICU for 3 or more days, intensive insulin treatment reduced in-hospital mortality (from 52.5% to 43.0%, $P = .009$). A 6-fold increase in severe hypoglycemic events (blood glucose < 40 mg/dL [2.2 mmol/L]) was observed in the intensively treated group (18.7% vs 3.1%), and hypoglycemia was identified as an independent risk factor for mortality [78].

The Glucontrol Trial [79], a prospective randomized controlled trial (RCT) in a mixed population of critically ill

patients, compared the effects of 2 regimens of insulin therapy aimed to achieve a blood glucose level between 80 and 110 mg/dL and between 140 and 180 mg/dL. The study was stopped prematurely because a high rate of unintended protocol violations and safety concerns. During treatment, the mean blood glucose was 118 vs 144 mg/dL. There were no differences in ICU mortality (16.97 vs 15.20), hospital mortality (24.6 vs 20.7), 28-day mortality (19.8 vs 16.1), or ICU length of stay (6 vs 6 days). The rate of hypoglycemia was greater in the intensified treatment regimen (8.6% vs 2.4%). Of interest, mortality among people with a blood glucose of less than 40 mg/dL during treatment was increased (32.6% vs 53.8%). The Efficacy of Volume Substitution and Insulin Therapy in Severe Sepsis (VISEP) Study [73], an RCT in 600 subjects with sepsis randomized to conventional (blood glucose 180–220 mg/dL) or to intensive insulin therapy (blood glucose 80–110 mg/dL), reported no decrease in 28-day mortality (26% vs 24.7%) and 90-day mortality (35.4% vs 39.7%), but reported higher rates of severe hypoglycemia with intensive insulin therapy (17% vs 4.1%; $P < .001$). Hypoglycemia (blood glucose < 40 mg/dL [< 2.2 mmol/L]) was identified as an independent risk factor for mortality (RR, 2.2 at 28 days; 95% confidence interval, 1.6–3.0) [73].

In a similar RCT, De La Rosa et al [74] reported that intensive glycemic control in a mixed medical-surgical ICU resulted in no decrease in morbidity or mortality, while increasing the rate of hypoglycemia 5-fold. The largest study to date, Normoglycemia in Intensive Care Evaluation Survival Using Glucose Algorithm Regulation trial compared outcomes among 6104 ICU patients randomized to an intensive glucose control (81–108 mg/dL) and conventional treatment (blood glucose 144–180 mg/dL) [75]. The 2 treatment groups showed good glycemic separation, with a mean absolute difference of 29 mg/dL in overall blood glucose levels (118 vs 145 mg/dL). They reported an absolute increase in the rate of the primary end point, death at 90 days, with intensive glucose control (27.5% vs 24.9% with conventional control; odds ratio, 1.14; $P = .02$). The rate of severe hypoglycemia (blood glucose < 40 mg/dL) was significantly higher in the intensive-control group than in the conventional-control group (6.8% vs 0.5%, $P < .001$) [69]. Two independently conducted meta-analyses of randomized studies comparing intensive insulin therapy with conventional management in the critically ill revealed that intensive insulin therapy conferred no mortality benefit but increased the risk of hypoglycemia [80,81]; although patients in surgical ICU appeared to benefit from tight glucose control [80].

8.3. Studies in medical and surgical patients in non-ICU settings

There are no RCTs examining the effect of intensive glycemic control on mortality and clinical outcomes in hospitalized patients in general medical/surgical settings. However, several observational studies point to a strong association between hyperglycemia and poor clinical outcomes, including prolonged hospital stay, infection, and disability after hospital discharge, and death [61,82–84]. In such patients, the presence of hyperglycemia is associated with prolonged hospital stay, infection, disability after hospital discharge, and death [61,62,65]. In a retrospective study of 1886 patients admitted

to a community hospital, mortality on the general floors was significantly higher in patients with newly diagnosed hyperglycemia and in those with known diabetes than in those who were normoglycemic (10% vs 1.7% vs 0.8%, $P < .01$) [61]. Admission hyperglycemia has also been linked to worse outcomes in patients with community-acquired pneumonia [85]. In a prospective cohort multicenter study of 2471 patients, those with admission glucose levels of greater than 11 mmol/L (198 mg/dL) had a greater risk of mortality and complications than those with glucose less than 11 mmol/L. The risk of in-hospital complications increased 3% for each 1 mmol/L increase in admission glucose. In a retrospective study of 348 patients with chronic obstructive pulmonary disease and respiratory tract infection, the relative risk of death was 2.10 in those with a blood glucose of 7 to 8.9 mmol/L, and 3.42 for those with a blood glucose of >9.0 mmol/L compared with patients with a blood glucose 6.0 mmol/L [86]. A 1 mmol/L (18 mg/dL) increase in blood glucose was associated with a 15% increase in the risk of an adverse clinical outcome, which was defined as death or length of stay of greater than 9 days.

8.4. Treatment options for achieving safe and effective glycemic control in the hospital

Insulin therapy is the preferred method of glycemic control most patients in the hospital setting [87]. In the ICU, IV infusion is the preferred route of insulin administration. Outside critical care units, subcutaneous insulin administration is used much more frequently. Oral agents have a limited role and should be avoided in the inpatient setting. In the critical care setting, continuous IV insulin infusion has been shown to be the most effective method for achieving specific glycemic targets [65,87]. Because of the very short half-life of circulating insulin, IV delivery allows rapid dosing adjustments to address alterations in patients' status. Numerous examples of successful continuous insulin infusion algorithms in achieving glycemic control are reported in the literature [63,66]. All published ICU insulin algorithms appear to be equally effective in controlling blood glucose without major clinical outcome differences, including frequency of severe hypoglycemic events, length of ICU and hospital stay, or mortality between different treatment algorithms [65,87].

Scheduled subcutaneous insulin is the preferred method for achieving and maintaining glucose control in non-ICU patients with diabetes or stress hyperglycemia. The recommended components of inpatient subcutaneous insulin regimens include a basal, nutritional (preprandial), and a supplemental (correction) component [65,87]. Hospitalized patients often require high insulin doses to achieve target glucose levels due to increased insulin resistance; thus, in addition to basal and nutritional insulin requirements, patients often require supplemental or correction insulin for treatment of hyperglycemia. Use of repeated doses of short-acting insulin per sliding scale, as a sole form of therapy in hospitalized patients with diabetes, should be avoided because of persistence of hyperglycemia in T2DM and risk of ketoacidosis in patients with type 1 diabetes [86].

8.5. In ambulatory patients (glycemic control and vascular events)

The implications of the UKPDS study was that tight glycemic and blood pressure control required a combination of agents with different sites of action and that a major number of patients would require insulin for blood glucose control [88]. It was also clearly shown that β -cell functions were depleted by approximately 50% in patients with newly diagnosed T2DM. Therefore, there was gradual progression of decline in β -cell function in T2DM. From the results of the UKPDS study, one may conclude that (1) intensive therapy to reduce glycemic excursion and control blood pressure reduces risk of complications; (2) neither insulin nor sulfonylurea therapy increases the risk of cardiovascular complication; and (3) T2DM is a progressive disease with relentless deterioration of β -cell function [89].

The findings of the UKPDS and the Kumamoto study [49] suggest that evidence exists for a relationship between microvascular diseases such as retinopathy, nephropathy, and neuropathy and good glycemic control. In addition, such intensive therapy would reduce the risk of coronary artery disease, stroke, and peripheral vascular disease. Furthermore, the Norfolk-Epic Study and the Australian Atherosclerosis Study showed an increasing risk of cardiovascular death in untreated persons with a hemoglobin A_{1c} level of 5.7% or greater [90,91].

The Action in Diabetes and Vascular Disease (ADVANCE), Action to Control Cardiovascular Risk in Diabetes (ACCORD), and Veterans Administration Diabetes Trial (VADT) trials were designed to determine the impact of tight glucose control and blood pressure control on the risk of macrovascular and microvascular complications in T2DM. The ACCORD study [92] involved more than 10 000 patients who had established cardiovascular disease or risk. These patients had a history of diabetes for 10 or more years. The intensively controlled groups achieved a hemoglobin A_{1c} level of 6.7% within 3 months and a stable value of 6.4% at 12 months. The control group achieved a hemoglobin A_{1c} average of 7.5%. The study involved multiple drugs; and there was clearly more weight gain, fluid retention, and hypoglycemic events in the intensively controlled group. The glycemic arm of the study was terminated after 3.5 years because of a 22% increase in all-mortality in the tightly controlled group. No individual drug appeared to account for the excess mortality; and patients who experienced severe hypoglycemia exhibited a higher mortality rate. Although patients randomized to intensive treatment arm had higher all-cause and cardiovascular mortality, they also experienced a significant reduction in nonfatal myocardial infarction. Results of the blood pressure and lipid arms of ACCORD demonstrated that in type 2 diabetic subjects at high risk for cardiovascular events, intensive blood pressure control targeting systolic blood pressure of 120 mm Hg did not reduce the rate of cardiovascular events compared to a targeted systolic blood pressure of 140 mm Hg [93]. Again, addition of fenofibrate to simvastatin monotherapy conferred no further reduction in cardiovascular events [94].

The ADVANCE (Action in Diabetes and Vascular Disease—Preterax and Diamicon Modified Released Controlled

Evaluation) [95] enrolled more than 11 000 patients who had known cardiovascular disease or at least one risk factor for cardiovascular and diabetes for 8 years. At baseline, only 1.5% of these patients were on insulin compared with 35% in the ACCORD trial. ADVANCE involved patients in 20 different countries including Canada, Russia, India, China, and Australia. It evaluated tight and conventional blood glucose and blood pressure control. All patients initially received an extended release of the sulfonylurea, gliclazide, with other orals added next, then basal insulin and finally bolus insulin. There was no forced titration in glucose adjustment. A 0.7% difference in hemoglobin A_{1c} was achieved between the tight and conventionally controlled groups. There was no increase in mortality between the groups, but there was not a statistically significant reduction in cardiovascular end points either. At 5 years, there was a significant reduction in macroalbuminuria, which may be predictive of a later reduction in cardiovascular events. Clinically significant hypoglycemia was not seen in the ADVANCE, giving evidence that a hemoglobin A_{1c} level of 6.5% can be achieved without high risk of adverse events [95].

The VADT [96] evaluated the rates of cardiovascular death, myocardial infarction, stroke, congestive heart failure, amputation for peripheral vascular disease, and interventions for peripheral vascular and cardiovascular disease in 1791 patients with identical treatment for other cardiovascular disease risk factors. The intensive control group achieved a hemoglobin A_{1c} level of 6.9% and the conventional control group achieved a hemoglobin A_{1c} level of 8.4%. There was a 13% reduction in cardiovascular end points, but this did not reach statistical significance. There was more hypoglycemia and sudden death in the intensively controlled group [96].

In summary, although secondary prevention trials do not show that reducing the hemoglobin A_{1c} level to less than 7% improved survival, they provide insight regarding the direction of future research in this area. First, it may take much more than 6 years to see cardiovascular reduction. Data 10 years after the intervention phase of the UKPDS showed no difference in glycemic control between the intensive and conventional treatment arms, but demonstrated that the reduction in microvascular disease was maintained, and that there was a 15% statistically significant reduction in myocardial infarction [97]. The Diabetes Control and Complications Trial/Epidemiology of Diabetes Interventions and Complications study [98] showed a 42% reduction in cardiovascular events seventeen years after the Diabetes Control and Complications Trial intervention in type 1 diabetic patients. The UKPDS finding suggests that cardiovascular risk reduction accrues over long duration of therapy, especially when intensive glycemic control is instituted early in the course of T2DM [97].

9. Postprandial hyperglycemia and cardiovascular disease

Reports from epidemiologic studies suggest that postprandial hyperglycemia is associated with increased cardiovascular risk independent of fasting hyperglycemia [6,99]. Furthermore,

some available evidence indicates that postprandial glycemic excursion may be a more dominant cardiovascular risk factor than fasting hyperglycemia [100,101]. In a meta-analysis of several studies with a pooled population of more than 95 000 subjects, the relative cardiovascular event risk was 1.33 in subjects with impaired fasting glucose compared to 1.58 in individuals with IGT [99]. Postprandial hyperglycemia has been demonstrated to correlate negatively with endothelial function in patients with T2DM [102].

Postprandial hyperglycemia can lead to vascular complications by several mechanisms including activation of nuclear factor κ B, which in turn can increase the expression of a number of genes in endothelial cells, monocyte-macrophages, and vascular smooth muscle cells [103]. Acute glycemic excursions have also been shown to elicit increased level of oxidative stress, which has been linked to endothelial dysfunction [104,105], production of thrombotic factors, pro-inflammatory cytokines, and lipid peroxidation [106].

The ADA recommends that individuals who have preprandial glucose values within target, but have hemoglobin A_{1c} values above target, should monitor postprandial glucose values 1 to 2 hours after the start of a meal [6]. The guidelines recommend postprandial glucose levels to not exceed 180 mg/dL during the 2 hours postmeal. Pharmacologic agents that preferentially target postprandial hyperglycemia include the meglitinides, α -glucosidase inhibitors, dipeptidyl peptidase-4 inhibitors, glucagon-like peptide-1 analogs and rapid-acting insulins. Although these agents can ameliorate postprandial hyperglycemia, it remains to be shown that they can reduce cardiovascular events in patients with T2DM.

The recently reported Nateglinide and Valsartan in Impaired Glucose Tolerance Outcomes Research examined the ability of short-acting insulin secretagogues in 9306 subjects with IGT and either cardiovascular disease or cardiovascular risk factors treated with nateglinide or placebo for 5 years [107]. This study showed that nateglinide offers no protection from the progression of IGT to diabetes or from the progression of cardiovascular disease including nonfatal myocardial infarction, nonfatal stroke, or hospitalization for heart failure. Thus, future long-term RCTs are needed to determine if reduction of postprandial glucose values may lower cardiovascular events.

10. Pharmacologic therapy for glycemic control

The choice of antiglycemic agents in T2DM should be guided by medical needs of the patient and treatment goals, potency of the agent in achieving optimum glycemic control, tolerability and side effect profile, ease of administration and convenience, cost-effectiveness, and other beneficial extraglycemic effects. Table 8 itemizes the different interventions available and their relative antihyperglycemic effect expressed as reduction in hemoglobin A_{1c} level. As monotherapy, most antidiabetic agents are able to reduce hemoglobin A_{1c} level by 0.5% to 2.0%, except insulin, which can reduce hemoglobin A_{1c} level by more than 3% [108]. Therefore, it is unlikely that any single agent will achieve the glycemic target in a patient with hemoglobin A_{1c} level of > 8.5%. However, some drug

Table 8 – Summary of glucose-lowering interventions [87]

Intervention	Expected decrease in hemoglobin A _{1c} with monotherapy (%)	Advantages	Disadvantages
Lifestyle to decrease weight and increase activity	1.0–2.0	Broad benefits	
Insulin	1.5–3.5	No dose limit, rapidly effective, improved lipid profile	One to four injections daily, monitoring, weight gain, hypoglycemia, analogues are expensive
Metformin	1.0–2.0	Modest weight loss	GI side effects, contraindicated with renal insufficiency
Sulfonylureas	1.0–2.0	Rapidly effective	Weight gain, hypoglycemia (especially with glibenclamide or chlorpropamide)
TZDs	0.5–1.4	Improved lipid profile (pioglitazone)	Fluid retention, CHF, weight gain, bone fractures, expensive,
GLP-1 analogs	0.5–1.0	Weight loss	Given by injection, frequent GI side effects, long-term safety not established, expensive
Other therapy α -Glucosidase inhibitors	0.5–0.8	Weight neutral	Frequent GI side effects, 3 times per day dosing, expensive
Glinides	0.5–1.5 ^a	Rapidly effective	Weight gain, 3 times per day dosing, hypoglycemia, expensive
Amylin Analogs	0.5–1.0	Weight loss	Three injections daily, frequent GI side effects, long-term safety not established, expensive
DPP-4 inhibitors	0.5–0.8	Weight neutral	Long-term safety not established, expensive
Emerging therapy Colsevelam	0.5–1	Antilipid properties	GI side effects
Ranolazine	0.6	No hypoglycemia, useful in angina	
Salsalate	–	Anti-inflammatory	
SGLT2 blockers	–		
Bromocriptine	0.6.	Useful in parkinsonism	

^a Repaglinide more effective in lowering hemoglobin A_{1c} level than nateglinide. CHF indicates congestive heart failure; GI, gastrointestinal.

combinations appear to be synergistic and can reduce hemoglobin A_{1c} by up to 3.5%.

10.1. α -Glucosidase inhibitors

The α -glucosidase inhibitors acarbose (Precose, Bayer Health-Care Pharmaceuticals Inc, Wayne, NJ) and miglitol (Glycet, Pfizer Inc., New York, NY) reduce the digestion of carbohydrates in the upper part of the small intestine, thus ameliorating postprandial hyperglycemia and enabling the β cells to compensate for the first phase insulin secretory defect in T2DM. However, the higher glucose load in the colon leads to gaseous distention and flatulence that some patients may tolerate poorly. α -Glucosidase inhibitors are administered at the beginning of each meal, and are contraindicated in patients with gastrointestinal disease such as inflammatory bowel disease, partial bowel obstruction, and in severe renal or hepatic disease. Furthermore, patients need to be cautioned to treat hypoglycemia with glucose as the digestion of complex sugars is inhibited with these agents. They are approved as monotherapy and in combination with metformin and sulfonylurea. They may be added to the therapy of patients with inadequate control on insulin. In the STOP-NIDDM trial, treatment with acarbose in subjects with prediabetes resulted in 25% relative risk reduction in the progression to T2DM and significant reduction in the risk of developing for cardiovascular disease [109].

10.2. Metformin

The biguanide metformin was introduced for the treatment of T2DM in Europe and Canada in 1957 but was not licensed in the United States until 1995 of because fear of lactic acidosis, a rare but fatal complication that was associated with phenformin, the first biguanide to be introduced. Lactic acidosis is estimated to occur in 1 case per 100 000 patients treated with metformin, especially in the setting of renal failure, with creatinine clearance of less than 30 mL/min [110]. Metformin improves islet cell responsiveness to a glucose load through the correction of glucose toxicity [111] and improves peripheral glucose utilization by enhancing muscle uptake of glucose, increased insulin receptor tyrosine kinase activity, and increased glut-4 translocation and transport activity. Metformin also reduces hepatic gluconeogenesis by inhibition of key enzymes in this pathway and mitochondrial depletion of the energy necessary for gluconeogenesis [112].

Metformin may have anorectic effects in humans and has been shown to inhibit leptin secretion via a mitogen-activated protein kinase signaling pathway in brown adipocytes [113]. Metformin was shown to reduce cardiovascular events in the UKPDS study [114], an effect that may be mediated via adenosine monophosphate-activated protein kinase-endothelial nitric oxide synthase (eNOS)-mediated signaling [115]. Metformin improves ovulation in insulin-

resistant women with polycystic ovarian disease [116] and may have long-term benefits of weight reduction and cardiovascular protection in diabetic patients who are treated with insulin [117]. It is equally efficacious in normal weight, overweight, and obese type 2 diabetic patients [118].

Metformin reduced the risk of progression from prediabetes to T2DM by 31% in the Diabetes Prevention Program (DPP) cohort [24], and the ADA consensus statement advocates the use of metformin in subjects with prediabetes who are not successful with LSM [6]. It is approved for use with α -glucosidase inhibitors, thiazolidinedione (TZDs), incretins including dipeptidyl peptidase IV inhibitors, and sulfonylureas. The optimum dose is 2000 mg a day. It can be expected to reduce the hemoglobin A_{1c} level by 0.8% to 2.0%. Metformin should be discontinued at the time of surgery and for 48 hours after administration of IV contrast. The main side effect of metformin is gastrointestinal upset with nausea and diarrhea. Given its cost-effectiveness and long-standing safety profile, metformin should be considered a first-line agent in the treatment of T2DM.

Recent population studies provide clues that the use of metformin may be associated with reduced incidence and improved prognosis of certain cancers. One study showed a lower risk of cancer diagnosis among diabetic patients using metformin compared with a control group of diabetic patients using other treatments [119]. A different study also showed lower cancer-specific mortality among subjects with diabetes using metformin compared with those treated with other antidiabetic agents [120]. As insulin and insulin-like growth factors stimulate proliferation of many normal and transformed cell types, agents that facilitate signaling through these receptors would be expected to enhance proliferation. A recent report showed that metformin acts as a growth inhibitor rather than an insulin sensitizer for epithelial cells. Breast cancer cells can be protected against metformin-induced growth inhibition by small interfering RNA against AMP kinase. This suggests that AMP kinase pathway activation by metformin, recently shown to be necessary for metformin inhibition of gluconeogenesis in hepatocytes, is also involved in metformin-induced growth inhibition of epithelial cells. The growth inhibition was associated with decreased mammalian target of rapamycin and S6 kinase activation and a general decrease in mRNA translation [121].

10.3. Thiazolidinediones

The currently marketed TZDs rosiglitazone (Avandia, Glaxo-SmithKline) and pioglitazone (Actos, Takeda Pharmaceuticals America Inc., Deerfield, IL) are approved for monotherapy and combination treatment of T2DM, and have been shown to reduce the risk of incident diabetes in subjects with prediabetes by more than 60% [122,123]. In addition, TZDs have been shown to preserve or improve β -cell secretory function in patients with T2DM while on active treatment [124] and adult-onset latent autoimmune diabetes [125]. There have been reports associating TZDs with increased incidence of cardiovascular events. In the PROactive study, pioglitazone conferred neither benefit nor harm on the predetermined cardiovascular end points compared with placebo. Whereas 2

meta-analyses have reported significant (40%) increase in the risk of myocardial infarction in patients treated with rosiglitazone [126,127], however, reanalysis by the FDA found no significant increase in serious ischemia in patients treated with rosiglitazone [128].

Furthermore, several prospective randomized studies in which subjects were treated with rosiglitazone including the Diabetes Reduction Assessment with Ramipril and Rosiglitazone Medication (DREAM) [122], A Diabetes Outcome Prevention Trial (ADOPT) [129], Rosiglitazone Evaluated for Cardiac Outcomes and Regulation of Glycaemia in Diabetes (RECORD) [130], ACCORD [92], and the VADT [96] did not report excess cardiovascular ischemic events. Further analysis of the data obtained from the VADT trial noted a 30% reduction in cardiovascular death and 70% reduction in events in the patients who received rosiglitazone [131]. Again, a retrospective analysis of the VA diabetes cohort that included nearly 40 000 patients treated with metformin, sulfonylurea, or TZDs found no difference in cardiovascular outcomes among users of the 3 classes of drugs [132]. It should be borne in mind that the small number of cardiovascular events in these studies, which may be a reflection of the effect of concurrent treatment with antihypertensives and antilipid agents, may have affected their outcome. An ongoing prospective, randomized, multicenter study, the Thiazolidinediones Intervention with vitamin D Evaluation is assessing the effect of rosiglitazone and pioglitazone on cardiovascular end points in type 2 diabetic patients at high risk for cardiovascular disease. Perhaps this trial may determine the risks or benefits of these agents; until then, the balance of available evidence is insufficient to ascribe reduced or increased risk of cardiovascular events to either of these agents.

Thiazolidinediones are associated with about 1% reduction in hemoglobin A_{1c}, weight gain, increased incidence of fluid retention and heart failure, and increased risk of fracture. Thiazolidinediones cause fluid retention via activation of sodium channels in the distal nephron. They should not be used in patients with New York Heart Association class 3 and 4 disease. Thiazolidinedione-induced sodium retention can be ameliorated with potassium-sparing diuretics or hydrochlorothiazide [133]. Fluid retention is exacerbated by insulin and may be associated with macular edema [134]. Liver dysfunction with TZDs is extremely rare; baseline liver function tests are recommended before initiation of treatment and may be repeated if clinically indicated. The TZDs have been found to be useful in patients with nonalcoholic steatohepatitis [135,136]. Several studies have linked the TZDs to osteoporosis and increased risk of fracture in distant long bones [137,138]. Therefore, it would be prudent to pay attention to bone mineral density in patients treated with TZDs, especially in individuals who have risk factors for osteoporosis.

More recent meta-analysis [139] showed an increased risk for myocardial infarction but not for cardiovascular mortality by rosiglitazone. Furthermore, retrospective analysis of the Medicare database demonstrated that in comparison with pioglitazone, rosiglitazone was associated with an increased risk of mortality in subjects older than 65 years, but did not elevate risk of coronary events [140]. On the other hand, other recently published data, including a post hoc analysis of the Bypass Angioplasty Revascularization Investigation 2 Diabetes

study, which is a prospective RCT, have not substantiated the finding of increased cardiovascular disease morbidity or mortality in patients treated with rosiglitazone [141,142]. Rosiglitazone is currently under review by the FDA, while the Thiazolidinediones Intervention with vitamin D Evaluation study is under partial hold. Given that the increased signal of cardiovascular disease demonstrated by meta-analyses and retrospective reviews have not been confirmed by prospective randomized studies, it would appear that an equipoise exists that would require a well-designed study to clarify.

In recent years, much progress has been achieved in the discovery and development of selective peroxisome proliferator-activated receptor (PPAR) γ modulators (SPPAR γ Ms) as safer alternatives to PPAR γ full agonists. Clinical and experimental data indicate that SPPAR γ Ms show less dissociation/recruitment of co-regulators, partial transactivation, and reduced potential for adipogenesis, with glucose uptake comparable to that of full agonists. In vivo, they exhibit effective insulin sensitization, often observed with significantly fewer side effects such as fluid retention, body weight gain, bone loss, and potential for carcinogenicity. Several SPPAR γ M preliminary clinical studies have demonstrated antidiabetic activity comparable to pioglitazone, with fewer or no adverse effects [143].

10.4. Incretins

Incretins are peptide hormones secreted by the enteroendocrine cells in the intestine that modulate glucose metabolism via their effect on pancreatic islet secretions. The gut hormones GLP-1 and glucose-dependent insulinotropic peptide (GIP) are incretins, which are rapidly inactivated by the enzyme dipeptidyl peptidase IV. The GLP-1 analogs exenatide and liraglutide evade rapid clearance by dipeptidyl peptidase IV; hence, they have a long half-life when injected subcutaneously. The analogs stimulate glucose-dependent insulin secretion and inhibit glucagon production, thus lowering hepatic glucose output. They also slow gastric emptying and promote early satiety and reduced food intake. Decreased food intake may be mediated locally by slowed gastric emptying and centrally by interacting with the area postrema [144]. The GLP-1 analogs are administered subcutaneously. Exenatide decreases hemoglobin A_{1c} level by approximately 1%, and can be used in combination with metformin, sulfonylureas, or TZDs. Glucagon-like peptide 1 analogs may produce hypoglycemia when used in combination with insulin secretagogues. Hence, the dose of the secretagogue should be reduced commensurately when used in conjunction with an insulin secretagogue.

Exenatide is currently approved for twice daily administration, but a weekly depot form is in development. The depot form of exenatide appears to have less nausea and vomiting, which is the most common side effect of incretin analogs [145]. The maximal dose of exenatide is 20 μ g a day. About a third of the drug is excreted by the kidney; therefore, it is contraindicated in patients with a CrCl of 30 mL/min or less. In suboptimally controlled T2DM, exenatide achieved equivalent control when compared with glargine but was associated with weight loss rather than with weight gain [146]. Studies comparing mixed insulin analog with exenatide have

obtained similar results [147]. Several cases of pancreatitis have been reported in patients treated with exenatide since it was approved by the FDA [148]. Ninety percent of these cases had other risk factors for pancreatitis including gallstones, high triglycerides, or alcohol abuse. Three cases were rechallenged and had nausea and vomiting but no pancreatitis. Type 2 diabetes increases the risk of pancreatitis 2.8-fold [149]; therefore, the risk with exenatide may not be higher than the elevated risk in diabetic patients. Emerging data suggest that GLP-1 analogs may be associated with improvement in such cardiovascular risks as elevated blood pressure and lipids [150,151], and in a porcine study, exenatide reduced infarct size by 40% [152]. Human studies on limiting infarct size with exenatide are currently underway.

Liraglutide is a GLP-1 analogue, which shares 97% structural homology with human GLP-1. However, unlike human GLP-1, which has a half-life of less than 5 minutes, liraglutide is able to evade degradation by dipeptidyl peptidase IV, which confers on it a half-life of about 13 hours [153]. It can be administered subcutaneously by a daily dose regimen of 1.8 mg. In clinical studies, treatment with liraglutide in patients with T2DM reduced hemoglobin A_{1c} by 1% to 1.6% [153,154]. Liraglutide has also been shown to produce dose-dependent weight loss and reduction in blood pressure in obese subjects [32]. Its main side effects are nausea and vomiting. Liraglutide (Victoza, Novo Nordisk, Princeton, NJ) was recently approved by the FDA for the treatment of T2DM. It is not recommended as initial therapy, and the label includes a black box warning about increased risk of medullary thyroid cancer. Studies in rodents have shown that liraglutide is associated with an increased risk of thyroid C-cell focal hyperplasia and C-cell tumors. In rodents, C-cell hyperplasia is considered a preneoplastic lesion leading to medullary thyroid cancer. Studies in rats and mice showed an increase in the occurrence of benign C-cell adenomas and malignant C-cell carcinomas at supraphysiologic doses [155]. Although these findings are troubling, their relevance to humans is unknown. In the controlled clinical trials, increases in calcitonin levels occurred in a slightly higher percentage of the patients treated with liraglutide than in control patients; however, calcitonin levels remained within normal ranges. Furthermore, data from a long-term study did not reveal any notable difference in mean calcitonin levels between liraglutide and control groups over 2 years of follow-up. The FDA concluded that increases in the incidence of carcinomas among rodents translated into a low risk for humans [156]. Another safety concern is a possible increased risk of pancreatitis. In the phase 2 and phase 3 trials of liraglutide, there were 7 cases of pancreatitis reported among the 4257 patients treated with liraglutide and only one case in the 2381 patients in the comparator group. The small number of events makes it difficult to draw conclusions about causation [156].

Dipeptidyl peptidase IV inhibitors prevent the degradation of native GLP-1, thereby giving rise to increased levels of this incretin. They are small molecules that can be absorbed orally. They are weight neutral and do not appear to impact gastric emptying or satiety [157]. The dipeptidyl peptidase IV inhibitors sitagliptin and saxagliptin have been approved for clinical use by the FDA. Sitagliptin and saxagliptin are administered as single oral dose of 100 and 5 mg daily, respectively; dose adjustment is required in patients with renal impairment to half the full dose if creatinine clearance is less than 50 mL/min

and further to 25 mg for sitagliptin if the CrCl is 30 mg/mL or less. Sitagliptin and saxagliptin are approved for monotherapy and in combination with other oral agents. As monotherapy, they reduce hemoglobin A_{1c} level by about 0.6%; but in combination with other oral agents, further hemoglobin A_{1c} level reduction can be achieved. Sitagliptin is available as a combination drug with metformin (Janumet, Merck & Co., Inc., West Point, PA).

10.5. *Pramlitide*

The incretin, pramlintide (Symlin, Amylin pharmaceuticals Inc., San Diego, CA), is an analog of the hormone amylin co-secreted by β cells with insulin. Amylin regulates gastric emptying, suppresses inappropriate glucagon secretion post meals, and increases satiety [158,159]. Pramlintide has similar effects and has been shown to promote weight loss in morbidly obese type 2 diabetic patients [160]. Symlin is indicated for T2DM, as an adjunct treatment in patients who have failed to achieve desired glucose control despite optimal insulin therapy, with or without a concurrent sulfonylurea agent and/or metformin. The main side effect of pramlitide is bloating, nausea, and vomiting. It is therefore started slowly—at 60 μ g before meals in T2DM. Patients on pramlitide and insulin are at a higher risk of hypoglycemia and should be instructed accordingly. A recent study indicates that pramlitide with each meal lowered the markers of oxidative stress along with the post-meal glucoses [161]. Another study showed that pramlintide plus basal insulin was as effective as basal/bolus insulin in controlling T2DM with an additional advantage of significant weight loss in patients treated with pramlintide [162].

10.6. *Insulin secretagogues*

Insulin secretagogues stimulate insulin secretion by the β cells of the pancreatic islet by interacting with the sulfonylurea receptor. They include the sulfonylureas and the glinides. The sulfonylureas are very commonly used because they are readily available, affordable, and have convenient dosing. The main side effect of the sulfonylureas is hypoglycemia, which can be more severe and prolonged than that produced by insulin, particularly when longer-acting formulations are used in the elderly [163]. They are also associated with weight gain. Sulfonylureas have a primary failure rate of 20% and a secondary failure rate of 5% to 10% per year of treatment probably due to apoptosis of β cells [164]. Patient allergic to sulfa-based antibiotics may cross-react to sulfonylureas. Although the sulfonylureas are not used in pregnancy, a study that compared insulin with glyburide therapy in gestational diabetes found the sulfonylurea to be equally efficacious and safe in this category of patients [165].

There are 2 types of sulfonylurea receptors, SUR1 and SUR2a/b; the latter are present in the myocardium and coronary smooth muscle where they function in close association with adenosine triphosphate-sensitive potassium channels that play a major role in ischemic preconditioning of the myocardium. The sulfonylureas bind predominantly to the SUR1 receptors present on the β cells but may also bind to the SUR2a/b receptors. Therefore, theoretically, the sulfonylureas could interfere with ability of the heart to adapt to ischemic

stress. Glimiperide exhibits a much lower affinity for the SUR2 receptor and should not affect ischemic preconditioning. It is noteworthy that clinical studies have not confirmed this theoretical possibility of worsened outcome in terms of cardiovascular disease in diabetic patients treated with sulfonylureas. Large prospective randomized clinical studies such as the ACCORD, ADOPT, DREAM, VADT, and RECORD did not report any increased cardiovascular mortality in patients treated with sulfonylureas. Although excess mortality in patients with myocardial infarction treated with sulfonylureas has not been proven, it would be prudent to avoid high-affinity SUR2 ligands in patients with myocardial hypoxia, especially because of the evidence that insulin infusion is beneficial in these patients.

Meglitinides bind to a different part of the sulfonylurea receptor than sulfonylurea drugs, which may mean less effect on ischemic preconditioning, but they may have the same effect on increasing β -cell apoptosis [166]. They have shorter serum half-lives and therefore a lower risk of hypoglycemia but must be administered immediately before each meal. The meglitinides (repaglinide, nateglinide, and mitiglinide) are less potent than the sulfonylurea drugs with repaglinide being the more potent of the two [167,168]. These drugs are ideally suited for combination use with metformin. They could also prove effective in combination with a TZD, a drug class that targets insulin resistance. Repaglinide is excreted primarily in the feces and does not require dose adjustment for renal failure; however, the glinides are metabolized via cytochrome P450 and have the potential for drug interactions and interaction with grapefruit juice. The maximum dose of repaglinide is 4 mg with each meal and the maximum dose of nateglinide is 120 mg with each meal. There is also a combination drug of repaglinide and metformin now on the market (Prandimet, Novo Nordisk).

10.7. *Insulin therapy*

Patients with T2DM have insulin resistance and progressive pancreatic β -cell failure, which results in deficient insulin secretion and consequent hyperglycemia and elevated free fatty acid level. The resulting glucotoxicity and lipotoxicity initiate a vicious cycle that further compromises ability of the β -cell to secrete insulin in response to hyperglycemia or oral hypoglycemic agents. Furthermore, the inexorable decline of pancreatic β -cell function in T2DM results in therapeutic failure of oral agents over time [113,122]. Thus, most patients with T2DM will ultimately require insulin therapy to achieve and maintain adequate glycemic control. Insulin is also indicated in the critically ill and hospitalized diabetic patient to maintain adequate glycemic control. Although early initiation of insulin therapy has been shown to be beneficial in inducing long-term glycemic control in newly diagnosed type 2 diabetic patients with severe hyperglycemia [169], about 50% of general practitioners delay initiation of insulin because of barriers [170]. Such barriers include fear of needles, weight gain, impact on lifestyle, and psychological effect. Inability to administer insulin due to poor dexterity or vision, narrow therapeutic window, and complex dosing, which could predispose to hypoglycemia, all add up to dissuade practitioners from commencing insulin therapy.

The pharmacokinetics of the available insulin preparations are shown in Table 3. In comparison with human insulin, the rapid and long-acting insulin analogs have the advantage of producing less hypoglycemia and weight gain, but are more expensive. The most efficacious way of initiating insulin therapy in type 2 diabetic patients who have failed treatment with oral agents remains a subject of study. The Treat-to-Target trial was a multicenter study in which 756 patients with uncontrolled T2DM (hemoglobin A_{1c}, 8.6%) treated with oral antidiabetic agents were randomized to receive either 10 U of NPH or insulin glargine at bedtime. Insulin dose was titrated upward weekly to target fasting blood glucose of 100 mg/dL [171]. After 24 weeks of treatment, both treatment arms attained an average hemoglobin A_{1c} level of 7%, with approximately 60% of the patients achieving the desired target hemoglobin A_{1c} level of less than 7% in both arms.

Although patients treated with NPH experienced slightly more episodes of hypoglycemia, both groups gained weight at the same rate (~3.0 kg). Other studies have adopted the treat-to target approach using insulin glargine plus oral agents vs human insulin 70/30 [172], glargine plus oral agents vs an analog mix of 70/30 plus oral agents [173], with reasonable degree of efficacy but considerably higher incidence of weight gain and hypoglycemia in patients treated with biphasic insulin. In the recently reported 3-year open-label, randomized, controlled, multicenter study, the Treating to Target in Type 2 diabetes (4T) trial compared the effect of adding basal insulin vs preprandial insulin vs biphasic insulin to metformin and sulfonylurea in patients who have failed oral therapy [174]. All 3 arms attained a comparable median hemoglobin A_{1c} level of approximately 7%, with patients treated with basal insulin experiencing less hypoglycemia and weight gain than the other treatment groups. It is noteworthy that the 4T trial used only insulin aspart for preprandial and biphasic arms and insulin detemir for the basal insulin group. It should also be noted that the addition of preprandial insulin to a sulfonylurea as was the case in the 4T trial may predispose to a higher incidence of hypoglycemia. Results of these prospective studies suggest that any one of the approaches adopted in these studies would be effective in achieving better glycemic control in the poorly controlled type 2 diabetic patient. The Treat-to-Target approach appears to have appeal due to simplicity and convenience for community use.

10.8. Emerging and investigational drug therapies

Colesevelam (Welchol, GelTex Pharmaceuticals Inc, MA), a bile acid sequestrant used for the treatment of hyperlipidemia, was recently approved by the FDA for the treatment of T2DM. The Glucose-Lowering Effect of WelChol Study showed overall hemoglobin A_{1c} level reduction of up to 1.0% in patients with baseline hemoglobin A_{1c} level greater than 8% over 12 weeks of treatment. This combined improvement in glycemic control and lipid profile gives colesevelam an advantage in the treatment of T2DM. It is administered orally, and its main side effects are gastrointestinal, particularly constipation. The mechanism of action is thought to be delayed or altered absorption of glucose in the intestines [175].

Ranolazine (Ranexa, Gilead Sciences Inc, Foster City, CA) is FDA approved for the treatment of angina. It is thought to

inhibit sodium potassium channels, which promote release of calcium. Recent data from the Metabolic Efficiency With Ranolazine for less Ischemia in Non-ST-Elevation Acute Coronary Syndrome-Thrombolysis in Myocardial Infarction 36 (MERLIN-TIMI) trial indicate that ranolazine reduces hemoglobin A_{1c} level by 0.6% over 4 months of therapy in patients who presented with diabetes and an acute coronary syndrome. It also reduced hemoglobin A_{1c} level and fasting glucose in nondiabetic patients. Ranolazine reduced the risk of recurrent ischemia and did not increase the risk of hypoglycemia [176].

Salsalate is an anti-inflammatory agent. The association between inflammation and T2DM is well established, and this anti-inflammatory agent has been known to reduce glycosuria in diabetic patients since the early 20th century. Aspirin has not found much clinical usage in this regard because of toxicity, but a related compound salsalate is currently being investigated for the treatment of T2DM. Salsalate has been shown to reduce levels of fasting glucose by 13%, post challenge glucose by 20%, and C-peptide by 34% compared with placebo. After 1 month of therapy, patients treated with salsalate reduced their glycated albumin values by 17%. There was also a 57% rise in adiponectin levels in patients treated with salsalate compared to placebo, indicating that this anti-inflammatory agent may offer promise in the treatment of diabetes [177].

Sodium-glucose transporter 2 (SGLT2) blockers are drugs that target the SGLT2, thus preventing renal glucose reabsorption and lower serum glucose by increasing the urinary excretion of glucose. This transporter protein is located exclusively in the proximal tubule of the kidney where 90% of glucose reabsorption takes place. Dapagliflozin, remogliflozin etabonate, and ISIS 388 626 are some of the drugs that inhibit SGLT2. Dapagliflozin has undergone phase 2 clinical trials, where minor side effects such as polyuria and weight loss were noted and there was increased incidence of bacterial urinary tract infections [178,179].

Bromocriptine has been shown to improve glycemic control and markers of insulin resistance in animal models of diabetes and obesity, an effect that has been duplicated in humans. A 1-year study that compared a quick release form of bromocriptine (Cycloset, VeroScience LLC, Tiverton, RI) with conventional modes of diabetes therapy showed that Cycloset reduced hemoglobin A_{1c} level by approximately 0.6% as monotherapy and 1.2% in combination with insulin or sulfonylurea. It also lowered plasma triglycerides and free fatty acids by approximately 30% [180].

Several new agents are in earlier stages of development for the management of diabetes. The development of structural and functional glucagon receptor antagonists represents a potential approach to decrease hepatic glucose production and attenuation of hyperglycemia in patients with diabetes [181]. Blocking glucagon action was recently reported in db/db mice using antisense oligonucleotide administration to reduce glucagon receptor expression in the liver, resulting in lower blood glucose, free fatty acids, and triglycerides, without the development of hypoglycemia [182]. Taking advantage of the homology between GLP-1 and glucagon, a GLP-1/glucagon hybrid peptide, dual-acting peptide for diabetes, agents with combined GLP-1 receptor agonist and glucagon receptor antagonist activity have been shown to reduce blood glucose

and to increase fasting glucagon levels with less gastrointestinal side effects than GLP1 analogs [183]. Glucokinase is an enzyme involved in the control of energy balance that plays a key role in glycolytic flux control. Glucokinase activators increase insulin release from pancreatic β cells and hepatic glucose utilization by modifying the activity of glucokinase, a key enzyme in glucose-sensing and glycemic regulation [184]. The role of glucokinase in glucose metabolism have been emphasized by loss-of-function mutations in the gene coding for glucokinase, linked to maturity-onset diabetes of the youth type 2 (MODY 2 characterized by impaired glucose responsiveness of β cells, decreased glycogen accumulation and increased hepatic glucose production after meals). Current studies are testing whether glucokinase activators will restore appropriated glucose sensing, that is, insulin secretion in response to glucose, hepatic glucose output, and GLP1 secretion [185]. Finally, the fuel sensor adenosine monophosphate-activated protein kinase in the hypothalamus regulates energy homeostasis by sensing nutritional and hormonal signals. Active laboratory research aims to determine if indirect activators of AMPKinase, acting at the mitochondrial level to decrease the phosphate ratio (adenosine triphosphate/ADP) may increase improve insulin secretion, excessive hepatic glucose production, and impaired glucose uptake by skeletal muscles [186].

11. Hypoglycemia in T2DM

Iatrogenic hypoglycemia is a frequent complication of intensive glycemic control in diabetes. Hypoglycemia, which may be defined as blood glucose level less than 70 mg/dL, remains the major rate-limiting factor in achieving optimum glycemic control in diabetic subjects [6]. It is associated with recurrent morbidity and sometimes mortality; and compromised defense against subsequent hypoglycemia by causing hypoglycemia-associated autonomic failure, defective glucose counterregulation, and hypoglycemia unawareness, thus creating a vicious cycle of recurrent hypoglycemia [187]. It may be difficult to estimate the absolute incidence of hypoglycemia in T2DM as some episodes may be asymptomatic. However, in the UKPDS, 2.4% of those using metformin, 3.3% of those using a sulfonylurea, and 11.2% of those using insulin reported major hypoglycemia over a 6-year period; furthermore, hypoglycemia was progressive, thus hindering adequate glycemic control [188]. Hypoglycemia may occur in type 2 diabetic patients treated with insulin or its secretagogues such as sulfonylurea or meglitinides. Insulin sensitizers such as metformin, TZDs, and incretins such as GLP-1 analogues and dipeptidyl peptidase IV inhibitors should not cause hypoglycemia when used as monotherapy. However, as the UKPDS data suggest, metformin may rarely cause hypoglycemia. As in hyperglycemic crises, hypoglycemia is associated with elevation of counterregulatory hormones, proinflammatory cytokines, lipid peroxidation, and oxidative stress [189]. Therefore, it is probable that hypoglycemia may also pose a cardiovascular risk.

Hypoglycemia should be treated with a carbohydrate containing 15 to 20 g of glucose in a conscious patient who is able to ingest without difficulty. Blood glucose should be checked in 15 minutes and treatment should be repeated if

hypoglycemia persists. Once blood glucose returns to normal, a patient should be encouraged to eat to prevent recurrent hypoglycemia. Patients who have significant risk of severe hypoglycemia should have their caregivers instructed on how to administer glucagon, which should be made available to such patients [6]. Diabetic subjects with hypoglycemia unawareness or recurrent severe hypoglycemia may benefit from raising their glycemic targets for several weeks to avoid hypoglycemia, in an attempt to reverse hypoglycemia unawareness [6,187]. Prevention of hypoglycemia remains an indispensable part of diabetes management. Education on proper use of pharmacologic agents especially insulin and its secretagogues, nutrition, and exercise are very important components of this process.

12. Preventive measures for T2DM

It is stated that the “highest calling of any health care provider is to prevent what he/she treats.” It is now clear through 3 landmark studies that LSM is effective in reducing the conversion of high-risk subjects with IGT to T2DM [24,25,190]. Furthermore, pharmacologic management with metformin prevented the conversion of IGT to T2DM in 31% compared with 58% for LSM [24]. The cost-effectiveness of LSM for all ages has been established, but similar calculations suggest that use of metformin for patients older than 65 years is not cost-effective because of lack of efficacy in this age group. With 57 million prediabetic individuals, consisting of 25.9% of the population, whose annual rate of conversion from prediabetes to T2DM is about 10% [24], there is a strong rationale to prevent development of diabetes and its complications with an aggressive approach.

In a follow-up study of DPP/Diabetes Prevention Program Outcomes Study (DPPOS) after 10 years [191], it would appear that the original LSM group lost 7 kg of body weight but gradually regained at a plateau of 2 kg, with metformin maintaining modest weight loss. The incidence of diabetes during DPP was 4.8 cases per 100 person-years for LSM, 7.8 in the metformin group, and 11 in the placebo group.

However, during the 10-year follow-up when patients in each group were offered LSM, it was interesting that during this period the incidence for T2DM fell to similar rates as that seen in the original LSM group where the incidence of diabetes cases per 100 person-years was 5.9 for lifestyle, 4.9 for metformin, and 5.6 for the placebo group. The diabetes incidence was reduced after 10 years to 38% in LSM and 18% in metformin compared with the placebo group, suggesting that the effect of these interventions will last for at least 10 years. As stated by Misra [192], the road for LSM is arduous, but it would appear that further studies are needed regarding types of diet and other pharmaceutical compounds that may prove more effective. Studies that evaluated the efficacy of lifestyle measures in preventing the incidence of T2DM such as the DPP [24] and the Finish Diabetes Prevention Study [190] considered lifestyle as a composite of weight loss, diet, and exercise. Therefore, it may be difficult to ascertain the effect of each of these measures. However, the Da Qing Study [25], which examined the effect of diet and exercise alone and in combination, demonstrated no significant difference in the

Table 9 – Prevention of T2DM

Completed trials	Intervention type	Risk reduction (%)	Reference
Da Qing	Diet	31	25
	Exercise	46	
	Diet + exercise	42	
Finnish Prevention DPP	Lifestyle	58	189
	Lifestyle	58	24,196
	Metformin	31	24,197
	Troglitazone	75	198
IDDP	Lifestyle	28.5	194
	Metformin	26.4	
	Lifestyle + metformin	28.2	
STOP NIDDM	Acarbose	25	109
TRIPOD	Troglitazone	56	195
XENDOS	Orlistat	37	29
DREAM	Rosiglitazone	60	122
	Ramipril	No effect	
NAVIGATOR	Nateglinide	No effect	107
	Valsartan	14	199
Trials in Progress			
ORIGIN	Insulin, glargine, ω -3 fatty acids	Ongoing	
NAVIGATOR indicates Nateglinide and Valsartan in Impaired Glucose Tolerance Outcomes Research.			

efficacy among the 3 intervention arms (relative risk reduction of 31%, 46% and 42%, respectively). Similarly, the Indian Diabetes Prevention Program found no difference among the groups treated with metformin and lifestyle alone and in combination—26.4% vs 28.5% vs 28.2%, respectively [193].

12.1. Other prevention programs

Table 9 outlines the completed trials using lifestyle modification and/or pharmacologic therapy to prevent diabetes [194–198].

13. The cost-effectiveness of lifestyle vs metformin or placebo in the DPP

The DPP conducted a series of studies to evaluate the costs associated with the primary prevention of T2DM in the DPP interventions to prevent or delay T2DM. In this first publication, the Diabetes Prevention Program Research Group [199] described direct medical costs, direct nonmedical costs, and indirect medical costs of placebo, metformin, and intensive lifestyle intervention over a 3-year study period of DPP. In this study research, costs were excluded.

“The direct medical cost of laboratory tests to identify one subject with impaired glucose tolerance (IGT) was \$139. Over 3 years, the direct medical costs of the interventions were \$79 per participant in the placebo group, \$2,542 in the metformin group, and \$2,780 in the lifestyle group. The direct medical costs of care outside the DPP were \$272 less

per participant in the metformin group and \$432 less in the lifestyle group compared with the placebo group. Direct nonmedical costs were \$9 less per participant in the metformin group and \$1,445 greater in the lifestyle group compared with the placebo group. Indirect costs were \$230 greater per participant in the metformin group and \$174 less in the lifestyle group compared with the placebo group. From the perspective of a health system, the cost of the metformin intervention relative to the placebo intervention was \$2,191 per participant and the cost of the lifestyle intervention was \$2,269 per participant over 3 years. From the perspective of society, the cost of the metformin intervention relative to the placebo intervention was \$2,412 per participant and the cost of the lifestyle intervention was \$3,540 per participant over 3 years.” [199]

The group reached the conclusion that “the metformin and lifestyle interventions are associated with modest incremental costs compared with the placebo intervention. The evaluation of costs relative to health benefits will determine the value of these interventions to health systems and society” [199].

14. Future research direction

The efficacy of intensive lifestyle modification in mitigating the progression from prediabetes to diabetes has been established in several studies [24,25,190]; however, it remains to be shown if the benefits of these interventions can be translated to individuals who are freely living in the community outside the tightly controlled research environment. Therefore, translational studies are pertinent in realizing the benefit of these landmark studies that should impact the diabetes epidemic positively. Furthermore, although the health risks of prediabetes are now well known by the scientific community, the general population is yet to appreciate the hazards of this condition. Hence, efforts aimed at disseminating information about this dysglycemic state, which is not innocuous, are pertinent. There is still need for pharmacologic agents that would ameliorate the glycemic burden in diabetes more effectively without producing undue side effects such as hypoglycemia. Although the time-tested older agents such as insulin, metformin, and sulfonylureas can reduce hemoglobin A_{1c} level by several points, intensive control with these agents is usually hampered by hypoglycemia. On the other hand, newer agents such as TZDs and incretins, which are less likely to produce hypoglycemia, do not possess very potent antidiabetic effects. This scenario has been complicated by the recent controversy about cardiovascular effects of some of the newer agents as highlighted in this review. Several studies mandated by the FDA evaluating the cardiovascular effects of some of these agents are currently ongoing.

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