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An Overview on Coronary Artery Disease and Diabetes Mellitus

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Abstract:

Diabetes mellitus (DM) and coronary artery disease (CAD) are closely related. DM is a risk factor for CAD, but it is also equivalent to established CAD. The prevalence of DM and CAD is growing primarily due to the rising prevalence of obesity. The rapidly changing life style, especially in developing countries, plays major role in the occurrence of these diseases.

Keywords: Coronary Artery Disease, Diabetes Mellitus, Myocardial Infarction.

Introduction:

Diabetes mellitus has reached epidemic proportions worldwide, and its prevalence is rising. The implications of a diagnosis of DM are as severe as a diagnosis of CAD (**1**).

Cardiovascular mortality in all age groups and for both sexes rises equivalently with DM or a history of myocardial infarction (MI) and the two are profoundly synergistic. In addition, DM (especially type 2 DM), is associated with clustered risk factors for cardiovascular disease (CVD) (**2**).

Among adults with DM there is a prevalence of 75% to 85% of hypertension, 70% to 80% for elevated low-density lipoprotein (LDL), and 60% to 70% for obesity (**3**).

CAD is the main cause of death in both type 1 and type 2 DM, and DM is associated with a 2 to 4-fold increased mortality risk from heart disease. Over 70% of people >65 years of age with DM will die from some form of heart disease or stroke. Furthermore, in patients with DM there is an increased mortality after MI, and worse overall long-term prognosis with CAD (**4**).

Diagnosis of diabetes mellitus:

The world health organization (WHO) defines impaired fasting glucose/impaired glucose tolerance as a fasting plasma glucose of 110–125 mg/dl and a 2-h plasma glucose determination after a 75-g glucose drink of 140 to 200 mg/dl. Diabetes is defined as a fasting plasma glucose that is greater than 126 mg/dl and a plasma glucose after a 75-g glucose drink that is greater than 200 mg/dl. The HbA1c, which reflects the average glycated hemoglobin during the prior 3 months, is greater than 6.5% in patients with diabetes mellitus (**5**).

Diabetes is present in a patient with classic symptoms of hyperglycemia or hyperglycemic crisis with a random plasma glucose greater than 200 mg/dl. The American Diabetes Association (ADA) criteria are slightly different in that impaired fasting glucose is defined as a fasting plasma glucose level between 100 and 125 mg/dl and impaired glucose tolerance is defined as a 2-h plasma glucose after a 75-g glucose drink between 140 and 199 mg/dl (**6**).

Predisposing factors for diabetes & cardiovascular disease:

1- Obesity:

The strongest risk factor for T2DM is excess body fat, due to high total fat intake, high consumption of sugar-sweetened beverages and physical inactivity. In general, a body mass index (BMI) of 25–29.9 kg/m2 is considered 'overweight' and a BMI ≥ 30 kg/m2 is considered obese (**7**).

An adolescent who is classified as obese at 18 years of age has more than a 50% risk of developing diabetes over their lifetime. This risk increases to greater than 75% in an adolescent classified as very obese (**8**).

Approximately 80% of individuals with T2DM are either overweight or obese. In these individuals, cardiovascular mortality increases by as much as 40% for every 5-unit increase in BMI above 25. With BMIs of 30–35 kg/m2, median survival is reduced by 2–4 years and at 40–45 kg/m2, median survival is reduced by 8–10 years **(9**).

2- Hypertension:

Hypertension is a common co-morbidity in patients with diabetes mellitus and is a major risk factor for cardiovascular disease. Adults with tight blood pressure control had a 34% reduction in the risk for myocardial infarction, sudden death, stroke and peripheral vascular disease and a 37% reduction in the risk of retinopathy requiring photocoagulation, vitreous hemorrhage and fatal or nonfatal renal failure compared with the less tightly controlled blood pressure group (**10**).

The American Heart Association/American College of Cardiology (AHA/ACC) guidelines recommend that in adults with diabetes (or at least one other cardiovascular risk factor) and hypertension, lifestyle changes and antihypertensive drug treatment be initiated at a blood pressure of 130/80 mmHg or higher with a treatment goal of less than 130/80 mm Hg if this goal can be accomplished without patient hypotension or syncope (**11**).

3- Dyslipidemia:

Patients with T2DM have an increased prevalence of lipid abnormalities that contribute to their high risk of cardiovascular disease. Analyses of patients with diabetes in large trials have showed significant primary and secondary prevention of atherosclerotic vascular events and death due to coronary artery disease with cholesterol-lowering therapy (**12**).

Meta-analyses of statin therapy, including data from over 18,000 patients with diabetes from 14 randomized trials with a mean follow-up of 4.3 years, demonstrate a 9% proportional reduction in all-cause mortality and 13% reduction in vascular mortality for each 39 mg/dl reduction in LDL cholesterol (**13**).

Patients treated with atorvastatin had an average 26% reduction in total cholesterol and 40% reduction in LDL cholesterol. In addition, the statin therapy group had 37% reduction in cardiovascular events, 27% reduction in all-cause mortality and 48% reduction in stroke as compared with the group treated with a placebo (**14**).

4- Tobacco smoking:

Tobacco smoking significantly increases the risk of T2DM and the risk of diabetes associated complications with the highest risk among heavy smokers. Moreover, studies of individuals with diabetes demonstrate that individuals who are exposed to second-hand tobacco smoke have an increased risk of cardiovascular disease, microvascular complications and premature death. Conversely, smoking cessation is associated with a significant decrease in microalbuminuria, blood pressure, dyslipidemia and insulin resistance (**15**).

Pathophysiology:

Hyperglycemia, excess free fatty acids and insulin-resistance increase oxidative stress, disrupt protein kinase C, intracellular signal transduction, increase advanced glycation end-products and activate receptors for advanced glycation end-production. As a consequence, there is decreased nitric oxide (NO) synthesis, thereby causing abnormalities in vascular endothelial cell function (**16**).

Disruption of protein kinase C signaling causes decreased vasodilation, impaired angiogenesis and increased leukocyte adhesion to vascular cells by inhibiting phosphoinositide 3-kinase (PI3K signaling). Receptors for advanced glycation end-production activation increase endothelial superoxide production, which decreases NO synthase activation and quenches NO production. Excess fatty acids and glucose contribute to mitochondrial dysfunction, an increase in free oxygen radicals and insulin resistance **(17**).

As a result, there is activation of nuclear factor-κβ and activator protein-1, increased production of vasoconstrictive endothelin-1, increased prothrombotic tissue factor and plasminogen activator inhibitor-1 (PAI-1) production that contribute to vascular inflammation, vasoconstriction and thrombosis (**18**).

Increased free fatty acids in diabetic patients activate Toll-like receptors that alter the ability of insulin-receptor substrate-1 to activate downstream targets PI3K and protein kinase B. These molecular events result in the downregulation of the glucose transporter GLUT-4 and result in insulin resistance. In addition, insulin resistance increases PAI-1 and fibrinogen and reduces tissue plasminogen activator concentrations, thereby facilitating vascular thrombosis(**16**).

Platelet aggregation is increased in the blood of diabetic patients due to increased expression of glycoprotein IIb/IIIa, which augment both platelet–von Willebrand factor and platelet–fibrin interactions and thrombosis. Hyperglycemia also impairs platelet calcium homeostasis by promoting calcium influx into platelets and thereby increases platelet activation and aggregation (**19**).

Adipose tissue in diabetes releases cytokines (adipokines) that include tumor necrosis factor alpha (TNF-α), interleukins (IL-1β and IL-6) and PAI-1, which contribute to chronic inflammation and thrombosis in diabetic patients. In addition, approximately 97% of patients with diabetes are dyslipidemic, which is highly correlated with atherosclerosis (**20**).

In diabetes, the predominant form of LDL cholesterol is the small, dense particle form, which is more atherogenic than large LDL particles. Small, dense LDL particles more easily penetrate and form strong attachments to the arterial wall and are more susceptible to oxidation. Oxidized LDL attracts monocytes to the intima of arterial vessels, which differentiate into macrophages, ingest oxidized LDL and differentiate into ‘foam cells’ in the intima (**18**).

Eventually, the foam cells undergo apoptosis, but the lipid accumulates in the vascular intima. Smooth muscle cells migrate from the vessel media into the intima and proliferate due to growth factors released from macrophages, endothelial cells and smooth muscle cells. Over time, there is a progressive accumulation of lipid and smooth muscle cells in the vessel intima and the formation of atherosclerotic plaques (**21**).

Cells in atherosclerotic plaques also produce proinflammatory factors such as monocyte chemotactic protein-1, macrophage colony-stimulating factor, inducible nitric oxide synthase and oxygen-free radicals that contribute to chronic inflammation, vascular cell damage and endothelial dysfunction (**22**).

However, some cytokines secreted by diabetic vascular endothelial cells decrease collagen synthesis by vascular smooth muscle cells and enhance the production of matrix metalloproteinases that lead to the breakdown of collagen. This increases tendency for vascular atherosclerotic plaques in diabetic patients to rupture and trigger vascular thrombosis (**23**).

Diabetic patients also have a significant dysregulation of micro RNAs (miRs) involved in angiogenesis, vascular repair and endothelial homeostasis that contribute to vascular disease. In this regard, miR-503 is upregulated and is critically involved in hyperglycemia-induced vascular endothelial dysfunction in ischemic limb muscles. In contrast, miR-126 expression is downregulated and is partially responsible for impaired vascular repair in patients with DM (**24**).

The hormonal and physiological abnormalities associated with diabetes mellitus including oxidative stress, endothelial dysfunction, alternations in mineral metabolism, increased inflammatory cytokine production and release of osteoprogenitor cells from the bone marrow into the circulation, which promote vascular intimal calcification (**21**).

Vascular smooth muscle cells can undergo osteogenic transformation into phenotypically distinct osteoblast-like cells that express and release osteochondrogenic proteins. In this regard, coronary artery calcification in diabetic patients correlates with total coronary artery plaque burden in addition to representing an independent risk factor for adverse cardiovascular outcomes (**25**).

Mechanisms involved in the pathogenesis of coronary artery disease in diabetic patients are summarized in figure 1.

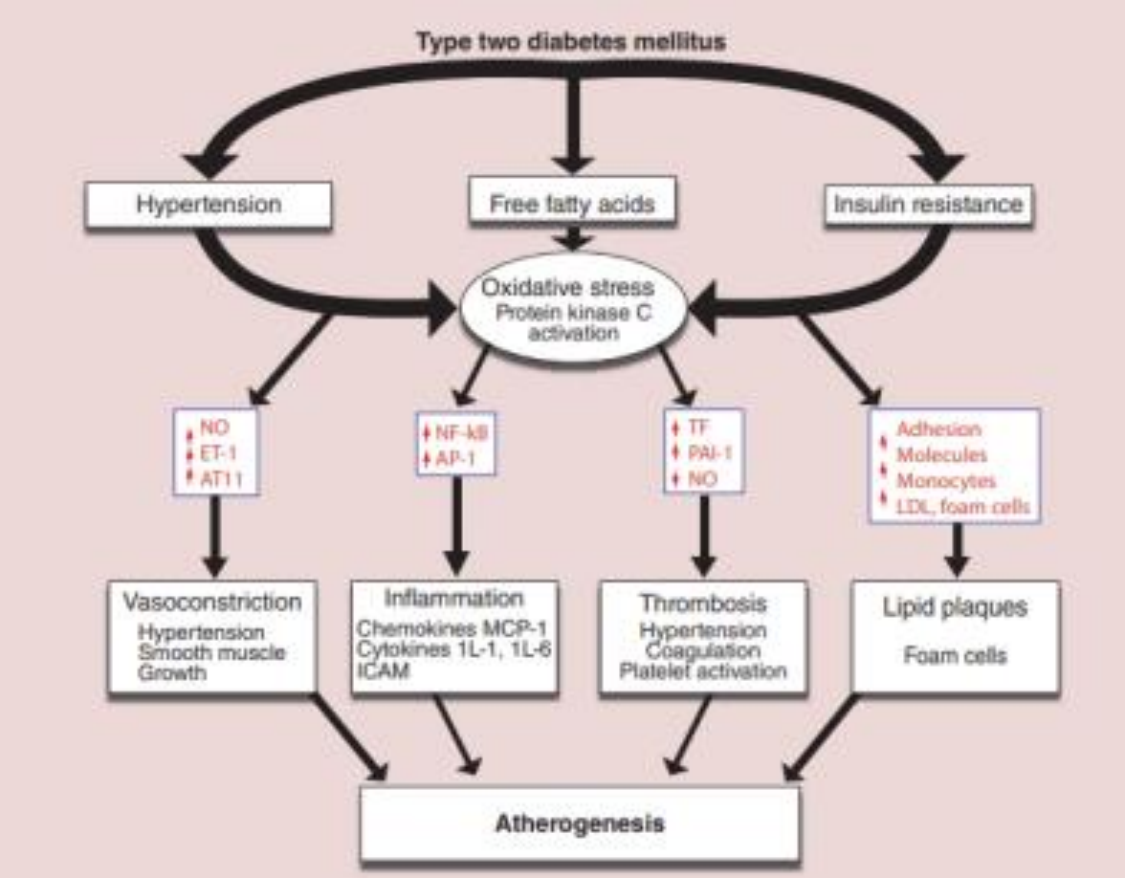

Figure (1): Pathophysiological mechanisms leading to atherosclerotic vascular disease in Type 2 diabetes mellitus. AP-1: Activator protein 1; AT II: Angiotensin II; ET-1: Endothelin-1; ICAM: Intercellular adhesion molecule; MCP: Monocyte chemoattractant protein; NF-κβ: Nuclear factor-κβ; NO: Nitric oxide; PAI-1: Plasminogen activator inhibitor-1; TF: Tissue factor (**2**).

Evaluation of CAD:

There are several modalities to evaluate for coronary artery disease including mainly electrocardiography (ECG), echocardiography (Echo), chest X-ray(CXR), Stress test, cardiac catheterization, and blood work. These tests are done depending on the context in which patients are presenting (**26**). The following are details on different diagnostic modalities we have available for the evaluation of coronary artery disease:

Electrocardiogram (ECG):

ECG is a very basic yet enormously helpful test in the evaluation of coronary artery disease. It measures electrical activity in the cardiac conduction system and is measured by 10 leads attached to the skin at standardized locations. It provides information about both the physiology and anatomy of the heart. It typically has 12 leads on the paper that is printed once the test is performed, and each lead correlates with the specific location of the heart (**27**).

Important information to notice on an ECG is a heart's rate, rhythm, and axis. After that, information regarding acute and chronic pathologic processes can be obtained. In acute coronary syndrome, one can see ST-segment changes and T wave changes. If an acute coronary syndrome (ACS) has degenerated into arrhythmias, that can also be seen. In chronic settings, ECG can show information like axis deviation, bundle branch blocks, and ventricular hypertrophy. ECG is also a cost-effective and readily available testing modality that is not user-dependent (**27**).

Echocardiography (ECHO):

Echo is an ultrasound of the heart. It is a useful and non-invasive mode of testing that is performed in both acute and chronic and inpatient and outpatient settings. In acute settings, it could tell about wall motion, valvular regurgitation and stenosis, infective or autoimmune lesions, and chamber sizes. It also is useful in the diagnosis of acute pulmonary pathologies like pulmonary embolism. It also evaluates the pericardial cavity (**28**).

In chronic settings, it can be done to see the same information mentioned above and also a response to the therapy. It also is used in an outpatient setting as part of stress testing. In addition to diagnostics, it also has a role in therapeutics for example, pericardiocentesis could be performed with the needle-guided by echocardiography. This test is user-dependent and could be costly compared to ECG (**15**).

Stress Test:

The stress test is a relatively non-invasive test to evaluate for coronary artery disease. It is used in the setting of suspected angina or angina equivalent and is helpful in ruling in or out coronary pathology when interpreted in an appropriate setting. During the test, the heart is artificially exposed to stress and if the patient gets certain abnormal ECG changes in ST segments or gets symptoms of angina, the test is aborted at that point and coronary artery disease is diagnosed (**29**).

ECGs are obtained before, during, and after the procedure, and the patient is continuously monitored for any symptoms. There are mainly two types of stress tests; exercise stress test and pharmacologic stress test. In exercise stress tests, the patient has to run on a treadmill until he achieves 85% of the age-predicted maximal heart rate. If a patient develops exertional hypotension, hypertension (>200/110 mmHg), ST-segment elevations or depression, or ventricular or supraventricular arrhythmias the test should be terminated (**15**).

Chest X-ray (CXR):

CXR is an important component of the initial evaluation of cardiac disease. The standard imaging films include standing posteroanterior (PA) and left lateral decubitus. Sometimes, anteroposterior (AP) projection is obtained especially in inpatient settings with the patient lying down, however, this interpretation of AP films is

significantly limited. Proper analysis of PA and AP views provides useful and cost-effective information about the heart, lungs, and vasculature. Interpretation should be done in a stepwise pattern so that important information is not overlooked (**26**).

Blood Work:

Blood work aids in establishing the diagnosis and assessing therapeutic responses. In acute settings, cardiac enzymes and B-type natriuretic peptides (BNP) are often done along with complete blood counts and metabolic panels. BNP provides information about volume overload of cardiogenic origin however it has its limitations. It can be falsely elevated in kidney diseases and falsely low in obesity (**30**).

Cardiac enzymes like creatine kinase (CK) and troponin provide information about an acute ischemic event. In chronic settings, lipid panel provides important prognostic information. C-reactive protein (CRP) and erythrocyte sedimentation rate (ESR) aid in assessing disease like acute pericarditis. Liver function tests (LFT) can be done to evaluate for an infiltrative process that can affect the liver and heart simultaneously like hemochromatosis. Liver tests are also done to assess increased right heart pressures, especially in chronic settings (**30**).

Cardiac Catheterization:

Cardiac catheterization is the gold standard and most accurate modality to evaluate ischemic coronary heart disease. It is however an invasive procedure with associated complications. Not everyone is a candidate for the procedure. In non-ACS settings, patients with higher pretest probability for CAD are usually the right candidates for it. In the ACS setting, all ST-elevation myocardial infarction (STEMI) patients and selected non-ST-elevation myocardial infarction (NSTEMI) patients get an emergent cardiac catheterization. This procedure is done in a cardiac catheterization laboratory (CATH LAB), is expertise dependent, and is done under moderate sedation. There is contrast exposure in the procedure which could cause serious allergic reactions and kidney injury (**31**).

Management of coronary artery disease in DM:

Several approaches were reported in the management of coronary artery disease in diabetic patients. These approaches aim to alter lifestyle behaviors, decrease weight, control blood glucose levels, restore normal lipid profile and maintain coronary health (**32**).

- **Weight loss**

Weight loss can improve cardiovascular risk and increase insulin sensitivity. 5% weight loss by lifestyle intervention is associated with an increase in HDL cholesterol, a reduction in triglycerides and a decrease in lipid-lowering medications in diabetic patients. Individualized nutrition guidelines are recommended for each patient with T2DM. In general, energy goals of 1200–1500 kcal per day should be considered for those patients weighing less than 114 kg and 1500–1800 for those patients weighing ≥114 kg (**33**).

Additional goals include restricting fat to less than 30% of total calories with less than 10% from saturated fat. Carbohydrate monitoring, consumption of fruits, legumes, vegetables, whole grains and dairy products, substituting healthy fats (e.g., monounsaturated fatty acids, polyunsaturated fatty acids) for saturated and trans fats and a Mediterranean style diet are recommended (**34**).

When lifestyle interventions for weight loss fail to achieve the desired goals, medications or surgery should be considered in addition to diet and an exercise program. Pharmacological therapy is indicated for individuals with a BMI of 25–30 kg/m2 with co-morbidities or a BMI greater than 30 kg/m2 with or without co-morbidities (**34**).

The AHA/ACC/Obesity Society guidelines recommend that adults with BMI ≥35 kg/m2 and significant obesity-related co-morbidities, such as atherosclerotic vascular disease, who are motivated to lose weight and who fail to lose weight on diet and weight loss medication be considered for bariatric surgery (**35**).

- **Physical activity:**

In order to improve patient physical fitness and HDL cholesterol concentrations and reduce HbA1c and waist circumference, 30 min of moderate-intensity aerobic activity at least 5 days per week for a total of 150 min or more is recommended. Alternative recommendations are 25 min of vigorous aerobic activity 3 days per week for a total of 75 min or more or a combination of moderate- and vigorous-intensity aerobic activity and moderate-to-high intensity muscle-strengthening activity for 2 or more days per week (**34**).

- **Smoking cessation:**

Although smoking cessation may be associated with weight gain, it was found that smoking cessation was associated with a decreased risk of cardiovascular disease over 6 years in patients with diabetes (**15**).

- **Lipid-lowering therapy:**

Patients with diabetes who are less than age of 40 years should take a statin medication, especially if they have clinical evidence of cardiovascular disease or an LDL cholesterol which is greater than 100 mg/dl. Diabetic patients greater than 40 years of age, in whom the 10-year cardiovascular risk is greater than 7.5% should be treated with lifestyle modification and a high-intensity statin medication, and patients with a 10-year atherosclerotic cardiovascular disease (ASCVD) risk less than 7.5% should be treated with life style modification and a moderate-intensity statin medication (**36**).

- **Hypertension treatment:**

Individuals with diabetes and a blood pressure greater than 115/75 mmHg are at increased risk for cardiovascular events and mortality. In addition, it has demonstrated in individuals with diabetes and confirmed hypertension that a reduction of ASCVD events occurs with a decrease in blood pressure to less than 140 mmHg systolic and less than 90 mmHg diastolic (**37**).

Consequently, patients with diabetes and hypertension should be treated to a systolic blood pressure goal of less than 140 mmHg and a diastolic blood pressure goal of less than 90 mmHg. A lower systolic and diastolic blood pressure target, such as ≤130/80 mmHg, is appropriate for individuals at high risk of ASCVD, especially stroke, if a lower blood pressure can be achieved without hypotension or syncope (**37**).

Weight reduction, sodium restriction and an angiotensin-converting enzyme (ACE) inhibitor or angiotensin receptor blocker (ARB), at the maximum tolerated dose indicated for blood pressure treatment, is the recommended first-line treatment for hypertension in patients with diabetes and albuminuria (**37**).

An ACE inhibitor or ARB significantly reduces the risk of patients with diabetes and albuminuria (≥300 mg/g creatinine) progressing to end-stage renal disease. Serum creatinine estimated glomerular filtration rate (eGFR) and serum potassium concentrations should be monitored in patients (**38**).

The use of ACE inhibitors and ARBs in combination is not recommended given the lack of added ASCVD benefit and the increased rate of hyperkalemia, syncope and acute kidney injury. Among patients without albuminuria for whom cardiovascular disease prevention is the primary goal of blood pressure control, a thiazide-like diuretic or dihydropyridine calcium channel blocker can be considered instead of or in addition to an ACE inhibitor or ARB (**39**).

- **Antiplatelet agents:**

Low-dose aspirin is recommended for the primary prevention of cardiovascular disease in men and women aged ≥50 years with diabetes and at least one additional major risk factor (family history of premature ASCVD, hypertension, dyslipidemia, smoking or chronic kidney disease/albuminuria) who are not at increased risk of bleeding. In patients with diabetes and history of myocardial infarction, 75–162 mg per day of aspirin is optimal therapy (**40**).

- **Insulin therapy:**

Insulin therapy is a cornerstone in managing diabetes mellitus (DM), particularly for patients who cannot achieve glycemic control with oral medications. However, its use in patients with both DM and cardiac conditions, such as heart failure or coronary artery disease, requires careful consideration due to potential risks and benefits (**41**).

Insulin helps regulate blood sugar levels, reducing the risk of complications like diabetic ketoacidosis and hyperglycemia, which can worsen cardiac conditions. However, insulin therapy may increase the risk of adverse cardiac events, such as heart failure exacerbations, especially in patients with pre-existing heart conditions (**42**).

Insulin therapy for diabetic patients with cardiac conditions is tailored to their specific needs, balancing glycemic control with cardiovascular safety. Long-acting insulins provide steady blood sugar control throughout the day and night and is ideal for maintaining fasting glucose levels. Rapid-acting insulins are taken before meals to manage postprandial (after-meal) glucose spikes. Premixed Insulin combines basal and bolus insulin in a single injection and is convenient for patients who prefer fewer injections but may lack flexibility in dosing. Multiple daily injections are combination of basal and bolus insulins administered separately and provides precise control but requires more frequent monitoring and injections (**42**).

Complications of insulin therapy in diabetic cardiac patients include hypoglycemia that may increase the risk of arrhythmias or other cardiovascular events. Insulin therapy can lead to weight gain and can promote sodium retention, which may exacerbate conditions like heart failure or increase cardiovascular risk. Insulin drives potassium into cells, which can lead to hypokalemia, increasing the risk of arrhythmias (**43**).

- **Glucose-lowering agents:**

The eight pathophysiological mechanisms that are targeted in these patients are: reduced insulin secretion from pancreatic β-cells, increased glucagon secretion from pancreatic α-cells, increased hepatic glucose production, neurotransmitter dysfunction and insulin resistance in the brain, increased lipolysis, increased renal glucose reabsorption, reduced incretin effect in the small intestine and reduced glucose uptake in skeletal muscle, liver and adipose tissue (**44**).

Diet, exercise and education are the foundation of any T2DM treatment program. The use of any drug in patients with T2DM must balance the glucose-lowering efficacy, the drug side effects, the dosing schedule, the requirements for glucose monitoring and the cost. The patient must participate with the physician in the decision-making process regarding which medications are selected and the intensiveness of blood glucose control (**6**).

The ADA's 'Standards of Medical Care in Diabetes' recommends in most patients with T2DM lowering the HbA1c to less than 7.0% to reduce the incidence of microvascular disease. This can be achieved with a mean plasma glucose of less than 150–160 mg/dl. The fasting and premeal glucose should be maintained at less than 130 mg/dl and the postprandial glucose at less than 180 mg/dl (**45**).

A more stringent HbA1C goal of less than 6.5% is recommended for individual patients with a short duration of diabetes, T2DM treated with lifestyle or metformin only, a long-life expectancy and no significant

cardiovascular disease. Less stringent HbA1c goals of greater than 7.5–8.0% are recommended for patients with advanced age and limited life expectancy, advanced diabetic complications, extensive co-morbid conditions, a history of severe hypoglycemia and those in whom the HbA1c target is difficult to attain despite intensive education and effective doses of multiple glucose-lowering agents, including insulin (**45**).

Metformin's proven safety record, neutral effect on body weight, benefits on cardiovascular outcomes and low cost make this drug optimal for monotherapy for T2DM patients. Metformin selectively inhibits mitochondrial glycerophosphate dehydrogenase, reduces cytosolic dihydroxyacetone phosphate and increases the cytosolic NADH/NAD ratio, which results in reduction in plasma glucose and lactate concentrations and reduces gluconeogenesis and hepatic glucose secretion. Metformin also may limit the desire for food intake possibly by glucagon-like peptide-1 (GLP-1)-mediated effect (**44**).

In circumstances where metformin is contraindicated or not tolerated, another oral agent should be used. The ADA/European Association for the Study of Diabetes currently recommend a second- or third-generation sulfonylurea, pioglitazone or dipeptidyl peptidase-4 (DPP-4) inhibitor when metformin cannot be used. Sulfonylureas increase insulin secretion by binding to the sulfonylurea receptor-1 in pancreatic β-cells, resulting in depolarization and calcium influx that initiates insulin secretion (**46**).

Thiazolidinediones (TZDs) preserve β-cell structure and function, reduce free fatty acid accumulation, decrease inflammatory cytokines and increase adiponectin concentrations, which lead to a decrease in insulin resistance and a decrease in β-cell failure. TZDs do not increase the risk of hypoglycemia and can be more long-lasting in their effectiveness than metformin or sulfonylureas (**47**).

GLP-1 receptor agonists activate GLP-1 receptors in the small intestine, causing increased glucose-dependent insulin secretion and glucagon suppression, delayed gastric emptying and appetite suppression. These actions result in improved glycemic control with minimal risk of hypoglycemia (**48**).

Sodium–glucose cotransporter-2 (SGLT2) inhibitors are approved for monotherapy but are currently used in combination with metformin and/or other hypoglycemic agents. Their mechanism of action involves inhibiting sodium-dependent glucose cotransporters in the proximal nephron of the kidney, thereby reducing glucose reabsorption and increasing urinary glucose excretion by up to 80 g/day (**49**).

In any patient not achieving a HbA1c target despite intensive therapy with two or possibly three oral glucose-lowering drugs, basal insulin should be considered an essential component of the treatment strategy. Basal insulin provides insulin coverage throughout the day and night by suppressing hepatic glucose production between meals and during sleep. However, hypoglycemia and weight gain remain the two significant side effects of intensive insulin therapy and severe hypoglycemia has been linked with increased cardiovascular morbidity and mortality(**45**).

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