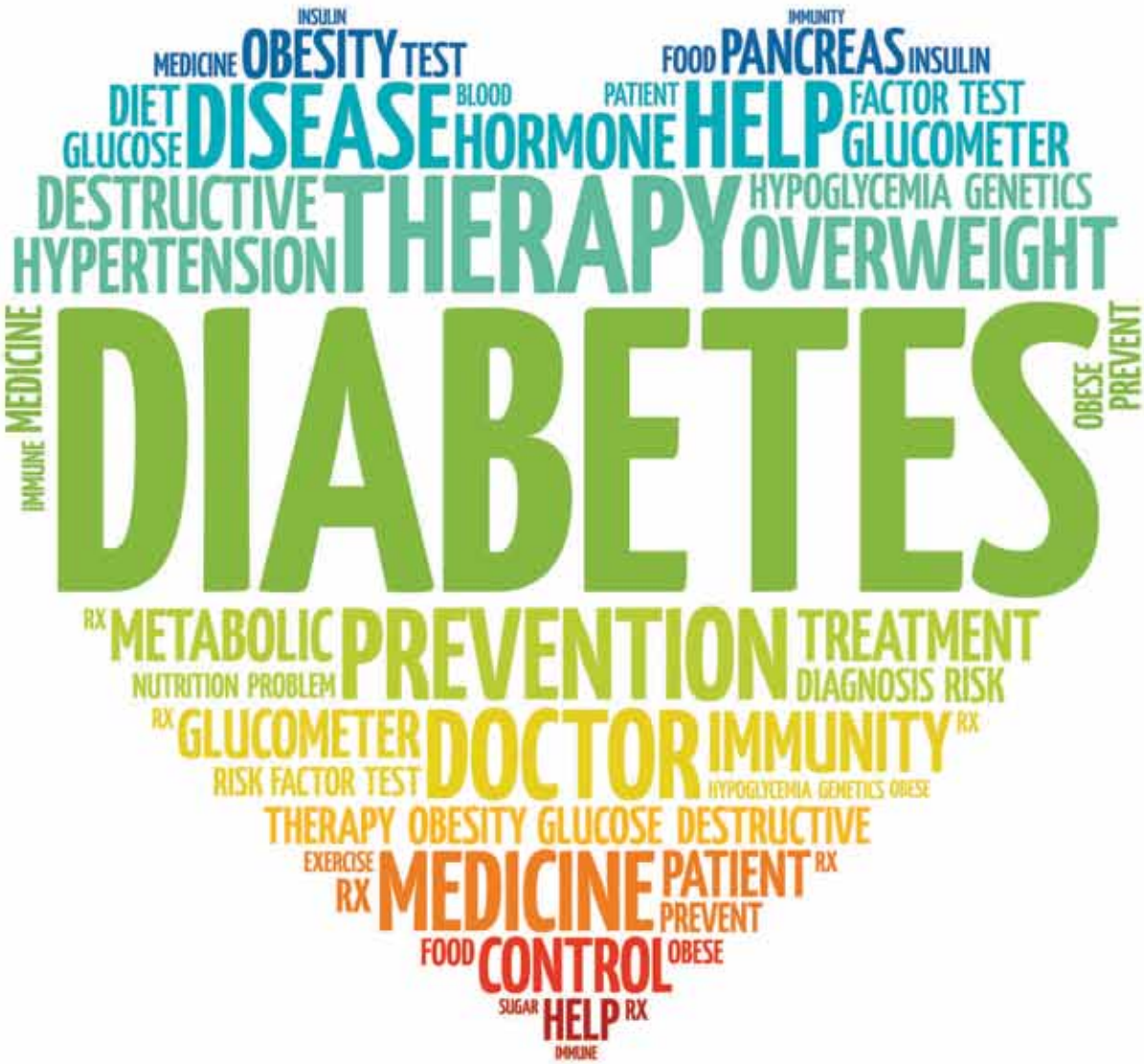
CONTINUING MEDICAL EDUCATION

TYPE 2 DIABETES



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Program Information

Needs assessment

Type 2 diabetes is a major chronic disease in both the developing and developed world, and has in fact been designated with the status of 'public health priority' in many countries. A large number of patients with type 2 diabetes remain asymptomatic for long, and therefore the disease often remains undetected for several years until it progresses to an advanced stage with resultant complications. This online CME activity is an attempt to apprise participants on the concepts related to development of diabetes and its complications, together with updated recommendations on its diagnosis and management, and the need for a holistic approach towards the disease.

Learning objectives

1. To familiarize with the rising burden of type 2 diabetes, and the mechanisms related to disease' development and its complications
2. To update on the recent recommendations for diagnosis and management of type 2 diabetes.

Target participants

Physicians

Method of participation in the program

- Study all parts of the educational activity
- Submit the posttest questions with answers
- A certificate of participation will be issued by **International Federation of Diabetes & Cardiometabolic disorders (IFDCD)** upon completing the posttest with a score of 60% or better.

Program activity

Release date: February 2021

Expiration date: April 2021

Course code: T2DPHC21

Contents

Type 2 Diabetes

Type 2 Diabetes

THE RISING BURDEN OF TYPE 2 DIABETES

Type 2 diabetes is a major chronic disease in both the developing and developed world, and has in fact been designated with the status of 'public health priority' in many countries.[1] This complex metabolic disorder is primarily known to affect the glucose homeostasis in human body,[2] and is characterized by presence of chronic hyperglycemia attributable to an underlying insulin resistance and defective insulin secretion. A large number of patients with type 2 diabetes remain asymptomatic for long, and therefore the disease often remains undetected for several years until it progresses to an advanced stage with resultant complications.

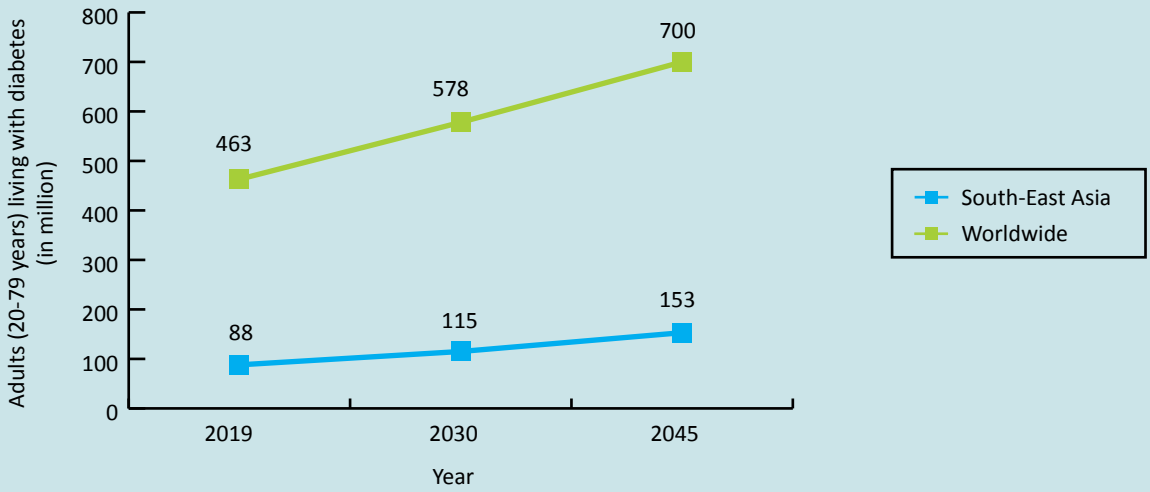
The prevalence of diabetes has risen rapidly in recent past, making it a pre-eminent global health challenge, with epidemic levels reached in several regions of the world.[3,4] Often, this enormous increase in the disease prevalence is attributed to changing lifestyle of the people and the resultant rising prevalence of obesity. Latest data given by the International Diabetes Federation (IDF) estimates that in 2019, approximately 463 million adults (20-79 years) were living with diabetes globally; and this number is estimated to increase to 578 million adults by 2030, and 700 million by 2045 (Figure 1). The corresponding number of people with diabetes in South-east Asia is estimated at 88 million (2019), 115 million (2030) and 153 million (2045).[5,6] Furthermore, the data suggests that 79% of adults with diabetes were living in low- and middle-income countries, with 1 in 6 adults with diabetes in the world coming from India. In addition, almost half of people with diabetes do not know that they have diabetes. Type 2 diabetes is the major contributor in this rising burden of diabetes, accounting for approximately 90-95% of all cases of diabetes.[7] These figures clearly provide an estimate of the rising prevalence of diabetes, and consequent public health threat and impact on the healthcare system.[8]

MECHANISMS RELATING TO DEVELOPMENT & PROGRESSION OF TYPE 2 DIABETES

Diabetes has a complex pathophysiology, with several risk factors, like genetic susceptibility and obesity contributing to the decreased insulin sensitivity in individuals and predisposing them to develop the disease. In the early phase of disease development, the pancreatic islet cells exert an adaptive mechanism in response to increasing insulin resistance by increasing the mass of pancreatic beta-cells and enhancing their function, thereby resulting in a state of compensatory hyperinsulinemia. Thus, the insulin resistance is offset by a sufficient release of insulin from the beta-cells, helping the body to maintain glucose homeostasis. However, when beta-cells are further challenged by the continuously rising insulin resistance, they fail to adequately compensate for the degree of insulin resistance, thus resulting in development of impaired glucose tolerance (IGT). Consequently, there is a progressive increase in the plasma glucose concentration, first postprandial and then fasting, leading to overt diabetes. Regarding beta-cell failure, it is now well-recognized that the event presents much earlier in the course of disease, and is well advanced by the time diabetes is recognized clinically.[9,10] In fact, some evidence suggests that about 50–80% of beta-cell function is lost by the time of clinical diagnosis of type 2 diabetes.[11] Additionally, there is development of diabetes-related complications like diabetic neuropathy in many of these patients.[12-15]

Overall, in concurrence to insulin resistance, impaired insulin secretion owing to a loss of beta-cells function, is the underlying defect in development of type 2 diabetes, and also determines the rate of disease progression.[9] These is a progressive increase in beta-cells dysfunction that continues and deteriorates further once there is apparent hyperglycemia, ultimately causing an exacerbation of the insulin resistance.[16,17] Such progressive increase

FIGURE 1 **Estimated burden (prevalence) of diabetes: Projections Worldwide and in South-East Asia**



Based on information from:

1. Diabetes facts & figures. International Diabetes Federation. Available at: https://idf.org/aboutdiabetes/what-is-diabetes/facts-figures.html [Accessed on: 23/01/2021].
2. IDF Diabetes Atlas. 9th edition 2019.South-East Asia. Available at: https://www.diabetesatlas.org/upload/resources/material/20191218_144626_sea_factsheet_en.pdf [Accessed on: 23/01/2021].

in beta-cells dysfunction contributes to deteriorating glycemic homeostasis and development of the diabetes complications. This late stage in disease continuum is significant with regards to clinical progression of diabetes and its outcomes.[18,19]

Conventional & Emerging Concepts Related to Natural History & Progression of Diabetes

Given the complex nature of diabetes, a variety of distinct pathophysiologic abnormalities are associated with it development and progression.[20] Nevertheless, as mentioned earlier, (a.) insulin resistance (with its reduced metabolic response), and (b) a deficient compensatory beta-cell insulin secretion (resulting in hyperglycemia) are the two core pathogenic mechanisms implicated in development of type 2 diabetes.[21] In this model, several genetic and environmental factors, e.g. obesity and lack of physical activity, greatly contribute to the insulin resistant state, which develops primarily in the skeletal muscles, liver and adipose cells.[9,21,22] In skeletal muscles, insulin resistance manifests as decreased glucose uptake after a carbohydrate meal, which occurs through post-receptor defects in the insulin action.[23] In the liver, despite a raised fasting insulin level, resistance to the action of insulin results in impaired suppression of hepatic glucose production, which, in cooperation with other metabolic factors contributes to amplified production of basal hepatic glucose.[14,22] Pancreatic beta-cells initially try to overcome increased insulin resistance and maintain normal glucose homeostasis by increasing the insulin secretion by increasing beta-cells mass and enhancing their function. However, when these cells fail to compensate for insulin resistance, there is development of IGT that finally progresses to overt hyperglycemia.[21] This development and persistence of chronic hyperglycemia in patients with diabetes leads to further failure of beta-cells owing to glucotoxicity, which in order, contributes to hyperglycemia; eventually, there is a vicious cycle of beta-cell deterioration.[24]

Thus, as a whole, progressive loss of the beta-cells' function and, to a relatively lesser extent, their reduced mass,results in the worsening glycemic control and

development of diabetes' complications.[25] The exact cause for a decline in function and mass of beta-cells in patients with diabetes is not completely understood, though several factors (genetic and environmental) are thought to contribute. Some evidence in this regard shows an age-related decline in the function of the beta-cells. Furthermore, as discussed earlier, insulin resistance related demand on the beta-cells to hypersecrete adequate insulin is also a cause for the progressive failure of the beta-cells. Glucotoxicity and lipotoxicity further contributes to the progressive decline in beta-cells. Chronic hyperglycemia causes impaired functioning of the beta-cells and also induces apoptosis through numerous mechanisms. In addition, genetic elements also play a role in the progression of the diabetes-related state. Hyperglycemia perpetuates a gradual decline in insulin gene expression with reduced insulin release.[14,16]

Chronic hyperglycemia also promotes endoplasmic reticulum (ER) synthesis of proinsulin, leading to ER stress and oxidative stress; the two closely entangled phenomenon, essentially involved in beta-cell dysfunction via direct effects on insulin biosynthesis and owing to consequences of the ER stress-induced unfolded protein response.[26] ER stress response in the patients is counteracted by intensified activation of the cellular pathway, unfolded protein response (UPR), responsible for maintaining ER homeostasis. However, a failure to reverse the ER stress often results in beta-cells dysfunction and apoptosis.[10,27,28] Accumulating evidence also suggests that amyloid deposition within the pancreas and hypersecretion of islet amyloid polypeptide (IAPP or amylin) also play an important role in the progressive failure of beta-cells.[14] IAPP, a major secretory product of pancreatic beta-cells, displays cytotoxic properties when aggregated and is believed to be involved in the loss of beta-cells in type 2 diabetes patients.[29]

Incretin hormones, which are released from the gastrointestinal tract (GIT) after a meal, have numerous protective effects on the beta-cells, for instance a reduction in apoptosis and enhancement of beta-cell proliferation and neogenesis.[30] These benefits are lost to considerably in patients with diabetes, thus demonstrating a role of impaired incretin system in the progressive failure of beta-cell. This dysfunction is characterized by a reduced concentration of the glucagon-like peptide 1 (GLP-1) and reduced sensitivity of beta-cells to the action of glucose-dependent insulinotropic peptide (GIP). Nonetheless, it is not exactly clear if these are the main events in the disease pathogenesis or occur secondary to glucose intolerance.[31,32] Individuals with IGT have a deficiency of the GLP-1 activity that further declines with the disease progression.

Deranged adipocyte metabolism is also suggested to have a role in the pathogenesis of type 2 diabetes. Obesity is often seen to be associated with dysfunctional adipose tissue that is characterized by presence of enlarged adipocytes, impaired insulin signaling, and resistance to the antilipolytic action of insulin. This results in raised levels of plasma free fatty acids (FFAs) due to lipolysis and ectopic deposition of the fat in the liver, muscle and pancreatic beta-cells (lipotoxicity),thereby potentiating insulin resistance in the liver and muscle, and impairing the insulin secretion.[33-35] The fat laden adipose tissue secrete several biologically active mediators (adipocytokines), which have also been known to play role in hepatic insulin resistance.[35-37] The release of adipocytokines contributes to development of a chronic low-grade pro-inflammatory state in the obese individuals, and also explain their heightened cardiovascular risk profile because of their involvement in pathophysiology of vascular diseases.[38,39] In addition, few other mechanisms also contribute to abnormal glucose homeostasis, for instance increased glucagon secretion from pancreatic alpha cells, increased resorption of renal glucose, and insulin resistance at the level of the brain. In all, in addition to the core insulin secretory defect, the development of diabetes is believed to be an outcome of a complex interaction of all the mentioned mechanisms.[12]

Role of oxidative stress in development of diabetes and its complications

In the pathologic milieu of diabetes, oxidative stress has been frequently associated with the disease development and progression, and its micro- and macro-vascular complications;possibly owing to the effects it exerts on pancreatic beta cells.[40-43] Oxidative stress occurs following an imbalance between the oxidative and anti-oxidative systems of the body, and this could mainly be attributable to an overproduction of the oxidative-free radicals and associated reactive oxygen species. In obese patients, excess calorie intake and a lack of physical activity

PATHOGENESIS OF TYPE 2 DIABETES: FROM TRIUMVIRATE TO OMINOUS OCTET

In type 2 diabetes, a failure of beta-cells together with development of insulin resistance in the liver and muscle represent the two main pathophysiological defects. However, emerging evidence now indicates that besides this triumvirate; at least 5 other systems contribute in the complex pathophysiology resulting in development of glucose intolerance in individuals with type 2 diabetes. These include dysfunction at the level of fat cells (accelerated lipolysis), gastrointestinal tract (incretin deficiency/resistance), alpha cells (hyperglucagonemia), kidney (increased glucose reabsorption), and the brain (insulin resistance). All these eight players collectively comprise the ominous octet, and signify the need of a holistic therapeutic approach – for e.g., combination drug therapy is initiated with diet/exercise - to address these inter-related pathophysiological defects.

More recently, the pathological construct seems to have progressed from the 'Ominous octet' to 'Egregious eleven', with inclusion of the role of stomach/small intestine, colon, and immune dysregulation/inflammation.

OMINOUS OCTET

PATHOPHYSIOLOGICAL PLAYERS IN TYPE 2 DIABETES

1. Beta-cell failure
2. Insulin resistance in muscle
3. Insulin resistance in liver

Triumvirate

4. Adipocyte resistance to insulin anti-lipolytic effect
5. Decreased incretin [glucagon-like peptide (GLP)-1/glucose-dependent insulinotropic polypeptide (GIP)] effect]
6. Increased glucagon secretion by alpha-cells
7. Enhanced renal glucose re-absorption
8. Central nervous system (CNS) resistance to anorectic effect of insulin

Based on information from:

1. DeFronzo RA. From the Triumvirate to the Ominous Octet: A New Paradigm for the Treatment of Type 2 Diabetes Mellitus. *Diabetes* 2009;58:773-795.
2. Defronzo RA , Eldor R, Abdul-ghani M. Pathophysiologic Approach to Therapy in Patients With Newly Diagnosed Type 2 Diabetes. *Diabetes Care* 2013;36(Suppl. 2): S127- S138.
3. Schwartz SS, Epstein S, Corkey BE, *et al.* A Unified Pathophysiological Construct of Diabetes and its Complications. *Trends in Endocrinology and Metabolism* 2017;28(9):1-11.

overloads the mitochondrial metabolism of glucose and fatty acids, resulting in the production of reactive oxygen species. Additionally, increased production of these reactive oxygen species in individuals with long-term diabetes may also be attributable to an increased overload of the advanced glycation end products (AGEs), the well-known pro-oxidative and pro-inflammatory compounds.[44] This amplified oxidative stress contributes to of pancreatic beta cells dysfunction, which are extremely susceptible to oxidative stress given a low expression of anti-oxidative enzymes and high endogenous production of reactive oxygen species.[45] Free radicals results in initiating a chain reaction, which further results in an increased inflammatory response and chemical modification of lipoproteins, which may augment the risk of atherogenesis and macrovascular complications in individuals with

type 2 diabetes. It therefore appears rational to propose that therapies targeted at reducing the oxidative stress might be a logical approach to not only help preventing the development of diabetes in at-risk individuals but also to impede the development of the disease related complications.[46-50]

PREDIABETES: AN IMPORTANT PHENOMENON IN THE NATURAL PROGRESSION OF DIABETES

"Prediabetes" is considered to represent a dysmetabolic state (neither normoglycemia nor true diabetes) that is associated with a very high risk for future development of diabetes.[51] The condition is often asymptomatic in nature, and characterized by an intermediate rise in levels of blood glucose, not reaching the threshold for making a diagnosis of diabetes. It may be further classified as two different conditions: i.e., impaired fasting glucose (IFG) and IGT;[21] presence of which indicates decreased insulin sensitivity,both in the periphery and the liver, and beta-cell decline. Eventually, the progressive deterioration in post-challenge and fasting glucose homeostasis marks the transition from prediabetes to diabetes.

Table 1 depicts the criteria for defining prediabetes as mentioned in the recent (2021) position statement of the American Diabetes Association (ADA).[7] The criteria clearly show that individuals with an HbA1c level of 5.7-6.4% may be considered to have prediabetes, and this could be significant clinically, given the often demonstrated association between the HbA1c values and risk of future diabetes. A systematic review of 16 studies showed that individuals with an HbA1c between 5.5 and 6.0% have a significantly greater risk of diabetes, with a 5-year incidence of diabetes ranging from 9 to 25%. Furthermore, the review showed that individuals with an HbA1c value of ≥6.0%, bear a 20-times higher risk of future diabetes than individuals with an HbA1c < 5%, with the 5-year risk of diabetes ranging from 25 to 50%.[52] Every year, an estimated 5-10% of individuals with prediabetes progress to diabetes. However, it is also important to this stage also renders an opportunity for timely interventions directed at halting the disease progression, and thus prevent development of overt diabetes. Lifestyle modification, which is the leading intervention in such individuals, can result in considerable risk reduction in this progression of prediabetes to diabetes. In addition, give the potential benefits of drug therapy in restoring normoglycemia in these individuals, this can also be considered.[53]

TABLE 1 **Criteria for defining prediabetes as mentioned in recent ADA 2021 standards of medical care in diabetes**

FPG 100 mg/dL to 125 mg/dL (IFG)
OR
2-h PG in the 75-g OGTT 140 mg/dL to 199 mg/dL (IGT)
OR
HbA1c 5.7–6.4%

*For all three tests, risk is continuous, extending from the lower limit of the range and becoming disproportionately higher at the upper limit of the range.

Based on information from: American Diabetes Association. Standards of Medical Care in Diabetes—2021. *Diabetes Care.* 2021;44(Supplement 1).

SCREENING FOR INDIVIDUALS AT INCREASED RISK OF DIABETES

The fact that many patients with type 2 diabetes often remain asymptomatic for long, and may remain undiagnosed until development of complications, provides a strong rationale for identifying such asymptomatic individuals those are at high risk of having diabetes.[54] Timely screening of individuals at high risk of diabetes helps in early diagnosis of the disease, and thus helps in preventing the development of complications. Also, as more people would be entered into the prevention programs, the number of people with diabetes could be reduced. Especially, screening seems prudent for individuals with risk factors associated with increasing risk of developing type 2 diabetes; for example, increasing age, obesity, and lack of physical activity. The recent ADA 2021 recommendations are that overweight or obese individuals with body mass index (BMI) ≥25 kg/m^2 having one or more risk factors for diabetes be screened for timely detection. For all people, however, (in those without risk factors), testing should begin at age 45 years (Table 2).[7] If the tests are normal, repeat testing at 3-year intervals may be reasonable; though yearly testing is recommended for those with prediabetes (A1C ≥5.7%).

DIAGNOSTIC AND MANAGEMENT APPROACHES FOR DIABETES

Traditionally, a diagnosis of diabetes is made based on the measurement of fasting plasma glucose (FPG) or the 2-h

TABLE 2 **ADA 2021 criteria for testing for prediabetes/diabetes in asymptomatic adults**

A. Consider testing in overweight or obese (BMI ≥25 kg/m² or ≥23 kg/m² in Asian Americans) adults who have ≥1 of the following risk factors:

i. First-degree relative with diabetes
ii. High-risk race/ethnicity
iii. History of cardiovascular disease (CVD)
iv. Hypertension
v. HDL-cholesterol level <35 mg/dL and/or a triglyceride level >250 mg/dL
vi. Women with polycystic ovary syndrome (PCOS)
vii. Lack of physical activity
viii. Clinical conditions associated with insulin resistance

B. Yearly testing should be considered in patients with prediabetes [A1C ≥5.7%, IGT, or IFG]

C. Women who were diagnosed with gestational diabetes mellitus should have lifelong testing at least every 3 years.

D. For all other patients, testing should begin at the age 45 years.

E. If results are normal - consider repeating the test at a minimum of 3-year intervals; though more frequent testing should be considered depending on the initial results and the risk status.

Based on information from: American Diabetes Association Standards of Medical Care in Diabetes 2021. *Diabetes Care* January 2021;44 (Supplement 1).

plasma glucose (2-h PG) after a 75-g oral glucose challenge. The A1c criterion, which represents an indirect measure of the average blood glucose levels, is also frequently added, being considered equally appropriate to above two tests (FPG and 2-h PG) for the diagnostic testing. Recent ADA 2021 recommendations mention HbA1c threshold value of ≥6.5% for the diagnosis of diabetes (Table 3). However, data demonstrate reduced sensitivity of this HbA1c threshold (≥6.5%) in diagnosing diabetes, showing that it diagnoses only 30% of the diabetes cases identified collectively using A1c, FPG, or 2-h PG.[7] Even so, the test is widely used owing to several advantages, like convenience, applicability, reproducibility and standardization of measurement, which appear to offset its lower sensitivity.[55,56]

TABLE 3 **ADA 2021 criteria for the diagnosis of diabetes**

FPG ≥ 126 mg/dL
OR
2-h PG ≥ 200 mg/dL during OGTT
OR
A1C ≥6.5%
OR
A random plasma glucose ≥ 200 mg/dL in a patient with classic symptoms of hyperglycemia or hyperglycemic crisis.

Based on information from: American Diabetes Association Standards of Medical Care in Diabetes 2021. *Diabetes Care*. January 2021;44 (Supplement 1).

MANAGEMENT OF DIABETES

Despite considerable advances been made in the treatment of type 2 diabetes, with evolution of a variety of drugs over the last several years;[57] yet,diabetes management remains a challenge. Many patients often fail to achieve the glycemic targets despite treatment. This could partly be related to compliance also given that optimal management of diabetes requires self-management skills also besides medications.[58] The goals of therapy however remains the same, i.e., achieving near normal blood glucose levels, slowing of disease progression and preventing the development of complications.[59,60] The progressive nature of the disease often requires use of more than one therapies.[61]

Glycemic goals in adults with type 2 diabetes

Recent ADA 2021 guidance on diabetes and its management mentions HbA1c <7% as a reasonable glycemic goal for most adults with type 2 diabetes.[7] Table 4 depicts the summary of glycemic recommendations for many non-pregnant adults with diabetes as provided by the ADA. The ADA updated recommendations advise more stringent target of HbA1c levels lower than the goal of 7% on the basis

TABLE 4 **ADA 2021 summary of glycemic recommendations for many adults with diabetes**

HbA1c	<7.0%[a]
Preprandial capillary plasma glucose	80–130 mg/dL[a]
Peak postprandial capillary plasma glucose[b]	<180 mg/dL[a]

[a]Less or more stringent glycemic goals may be appropriate for individual patients.
[b]Postprandial glucose measurements should be made 1–2 h after the beginning of the meal, generally peak levels in patients with diabetes.

Based on information from: American Diabetes Association Standards of Medical Care in Diabetes 2021. *Diabetes Care.* January 2021;44 (Supplement 1).

of provider judgment and patient preference, if it can be achieved safely without significant hypoglycemia or other adverse effects of treatment. In contrast, less stringent A1C goals (such as <8%) may be appropriate for patients with limited life expectancy, or where treatment harms overweigh the benefits. In all, a patient-centered approach is required when setting the glycemic targets in individual patients, based on key patient characteristics, and to safely maximize benefit and minimize risk of hypoglycemia. Herein, opting for the less complex regimens with no/minimal adverse effects, which can achieve the desired glycemic target,may be preferable.[62]

Lifestyle interventions

Both dietary modifications and exercise form the part of lifestyle interventions that have been found vital in the management of patients with diabetes owing to their positive effects on the HbA1c indices.[63,64] Medical nutrition therapy is an important component of the healthy lifestyle that helps to achieve the goals of improving overall metabolic measures beyond calorie restriction and weight loss.65 It been shown to promote sustained reduction in HbA1c in patients with diabetes, while also improving the lipid profile and blood pressure. The dietary advice can be tailored and individualized as per the patient's requirements. Intake of high-fiber food and low-fat dairy products have been shown to improve glycemic control; while food items with saturated fats, snacks and sweets should be consumed in considerably reduced quantities and less frequently. In all, diabetic patients should be counseled periodically and encouraged to adopt therapeutic lifestyle changes. Nutrients (multivitamin) supplementation may be required in select populations, including older adults, vegetarians, and people following very low-calorie or low-carbohydrate diets.[7]

Besides diet modification, physical activity is another important component of lifestyle modifications in patients with diabetes and pre-diabetes, shown to aid in the prevention and management of these metabolic disorders. The recent ADA 2021 recommendations suggest that most adults with type 2 diabetes should engage in ≥150 min of moderate-to-vigorous intensity aerobic activity per week, spread over at least 3 days/week, with no more than 2 consecutive days without activity.[7] Adults with type 2 diabetes should also decrease the amount of time spent in daily sedentary behavior; and interrupt prolonged sitting every 30 min for blood glucose benefits. Balance training and flexibility training are recommended 2–3 times per week for older adults with diabetes.

Drug therapy

While lifestyle modifications may be the only interventions required for initial 3-6 months in patients with near target HbA1c; eventually, progression to the drug therapy is needed if therapeutic targets are not achieved.[59,62] A variety of oral antidiabetic agents, from several classes, are available, for use in such patients. These include biguanides, sulfonylureas, meglitinides, thiazolidinediones dipeptidyl peptidase (DPP)-4 inhibitors, alpha-glucosidase inhibitors and SGLT2 inhibitors.[22,62] Generally, metformin is the initial pharmacological choice, when not contraindicated, because of its ability to suppress the hepatic glucose production. In fact, this is used as monotherapy in conjunction with lifestyle modifications for most patients with diabetes; once initiated, it should be continued as long as it is tolerated and not contraindicated.[7] Sulfonylureas, another group of oral hypoglycemic agents, are insulin secretagogues; whereas glucagon-like peptide-1 (GLP-1) receptor agonists and thiazolidinediones support and enhance the beta-cells function.

In general, when selecting the anti-hyperglycemic regimen in adults with type 2 diabetes, a patient-centered approach is recommended, which should be based drug-specific like efficacy, risk of hypoglycemia, effect on weight, and patient related factors like presence of comorbidities. Regarding an effect on weight, weight gain is common with sulfonylureas, while DPP-4 inhibitors are weight-neutral, and drugs like SGLT2 inhibitors and

Box 1: ADA 2021 screening recommendations for common complications of diabetes

- Consider investigations for coronary artery disease (CAD) in presence of any of the following:
  - » Atypical cardiac symptoms (e.g., chest discomfort,unexplained dyspnea);
  - » Signs or symptoms of associated vascular disease, including transient ischemic attack (TIA), stroke,carotid bruits, claudication, or peripheral arterial disease (PAD); or
  - » Electrocardiogram (ECG) abnormalities (e.g., Q waves).
- Assess urinary albumin and estimated glomerular filtration rate (eGFR) at least once a year in all patients with type 2 diabetes.
- Assess all patients for diabetic peripheral neuropathy starting at diagnosis of type 2 diabetes and at least annually thereafter.
- Assessment for distal symmetric polyneuropathy should include a careful history and assessment of either temperature or pinprick sensation and vibration sensation using a 128-Hz tuning fork.
- Consider an initial dilated and comprehensive eye examination by an ophthalmologist/optometrist at the time of diagnosis of type 2 diabetes. If there is no evidence of retinopathy for $1 annual eye exam and glycemia is well controlled, consider exams every 1–2 years. If any level of diabetic retinopathy is present, repeat subsequent dilated retinal examinations at least annually. More frequent examinations will be required if retinopathy is progressing or sight-threatening.

Based on information from: American Diabetes Association Standards of Medical Care in Diabetes 2021. *Diabetes Care*. January 2021;44 (Supplement 1).

GLP-1 receptor agonists help in inducing weight loss.[7,66] Given an inadequacy of any single drug in addressing all the pathophysiological defects of diabetes; a combination of two or three drugs is sequentially engaged if patient is not able to achieve the glycemic targets after a set interval. However, it may not be rational to delay treatment intensification for patients not meeting treatment goals; as a stepped-care approach may not aptly address the multiple pathophysiological mechanisms contributing to development of diabetes and progressive beta-cell demise (glucolipotoxicity). an early use of the combination of agents with complementary mechanisms of action highlights the pathophysiological approach, and has also been incorporated into the updated guidelines. Recent ADA 2021 recommendations in fact suggest considering dual therapy initiation in patients with newly diagnosed type 2 diabetes who have A1c ≥1.5% above their glycemic target.[7]

Insulin therapy is usually introduced as a later option to prevent progressive dysfunction of beta-cells unless there is metabolic decompensation, which may necessitate its early use. An early introduction of insulin should be considered if there is evidence of ongoing catabolism (weight loss), if there are symptoms of hyperglycemia, or when blood glucose levels (≥300 mg/dL) or A1c levels (>10%)are very high.[7]

COMPLICATIONS IN PATIENTS WITH UNCONTROLLED DIABETES

Patients with type 2 diabetes are at a high risk of several complications, mainly attributable to the progressive nature of the disease and the effect of inadequate glycemic control, which result in injurious effects of hyperglycemia. Largely, these complications are divided into: (i) macrovascular complications [coronary artery disease (CAD), peripheral arterial disease (PAD), and stroke)], and (ii) microvascular complications (diabetic neuropathy, nephropathy and retinopathy).[67,68] Both macrovascular and microvascular complications contribute to significant morbidity and mortality in patients with type 2 diabetes, making it important for the physicians to understand this relationship of diabetes and its complications; box 1 shows ADA 2021 screening recommendations for common complications in patients with type 2 diabetes.[7] This need could be particularly important

in the Indian scenario, where susceptibility of people to complications of diabetes differs from that of white populations and control of diabetes is far from ideal; with a mean HbA1c of 9.0% that is at least 2.0% higher than suggested by the international bodies.[69,70]

Mechanisms relating diabetes complications

Similar to the disease, the exact pathophysiology of its complications is presumed to be complex, and remains ill-defined despite extensive work done. A number of mechanisms have been alleged contributing to the high risk of complications in patients with type 2 diabetes, including chronic hyperglycemia, diabetic dyslipidemia, and inflammation. Hyperglycemia, the core metabolic abnormality in diabetes, is suggested as the chief mediator of its macro- and microvascular complications, together with a key role played by the oxidative stress. In fact, oxidative stress could be a common activator of the metabolic pathways, which mediate the onset of diabetic complications. Hyperglycemia results in a disproportionate increase in the superoxide production in the endothelial cells, which contributes to oxidative stress and activates several interlinked pathways of glucose metabolism linked,either directly or indirectly,to diabetic complications.[71-79] Some of the pathways implicated in diabetes complication include the polyol pathway flux, overactive hexosamaine pathway, activation of protein kinase C, and a markedly accelerated production of the advanced glycation end products (AGEs).

POTENTIAL OF ADJUVANT THERAPY IN DIABETES

Although several new and effective drug therapies have been developed for type 2 diabetes, the disease and its complications still remain major medical challenges.[80] In this regard, the multifaceted nature of diabetes and its complications, for instance an increased accumulation of the AGEs and increased oxidative stress contributing to the pathogenesis, has prompted investigations into the use of several adjunctive therapeutic approach for diabetes, besides the conventional drug therapy.[81-83] For instance, resveratrol, a stilbene compound and a phytoalexin synthesized by plants, has been reported to have anti-hyperglycemic and other protective effects in diabetes, exerted via several mechanisms; such as an increased action of the glucose transporter in cytoplasmic membrane, enhanced adiponectin levels, and an activation of the SIRT1 homolog silent information regulatory 2 (Sir2), thus mimicking the benefits of calorie restriction.[84] A systematic review and meta-analysis assessing the effects of resveratrol on glycemic control and insulin sensitivity among patients with type 2 diabetes also suggested that supplementation of resveratrol may benefit the management of type 2 diabetes.[85] Curcumin, the active ingredient in turmeric, has also caught attention for potential use in the prevention and treatment of diabetes and its complications, possibly because it could favorably affect most of the leading aspects of diabetes, including insulin resistance, hyperglycemia, and islet apoptosis.[86,87] Likewise, *Pterocarpus marsupium* (*P. marsupium*), an Indian traditional plant derivative, has also been reported as a highly effective blood glucose lowering agent, with its glycemic effect being comparable as add-on therapy in patients with type 2 diabetes.[88] These agents could potentially be used as adjuvants, together with conventional drug therapy, with intent to better target the multifaceted pathophysiological abnormalities underlying diabetes.

SUMMARY

The relentless rise in the worldwide prevalence of diabetes poses a major healthcare challenge, especially in the developing nations. A number of factors could be accountable for this rising burden. Many patients with diabetes are often asymptomatic for a long time before progressing to the clinically overt form; with progression to complications being faster in those with suboptimal control of diabetes. This makes it rational to not only have a clear understanding of the disease and its course, but also underlying pathophysiologic process, so that more targeted and tailored therapies can be offered to individual patients. The recent ADA 2021 guidelines provide update recommendations on the screening, diagnosis and management of individuals with diabetes and pre-diabetes, which can be used as a framework for applications in clinical practice. Besides conventional drug regimen, the multifaceted nature of diabetes and its complications has prompted investigations into use of adjunctive therapies for diabetes, which may be considered on an individualized basis for a more holistic approach towards the disease control.

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