Diabetes: Pathophysiology, Comorbidities, and Clinical Management

Overview of network modelling approaches and virus- or immunotherapy-induced diabetes with guidelines

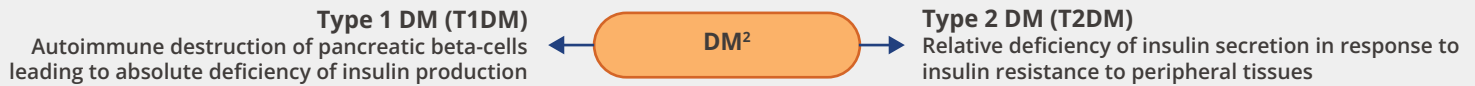## Overview of diabetes mellitus (DM)

DM is a chronic disease characterised by elevated levels of blood glucose that can cause damage to the heart, vasculature, kidneys, nerves, and eyes over time[1]

In 2019, diabetes caused 4.2 million deaths[2]

Its increasing global prevalence is a serious concern[2]

Type 1 DM (T1DM)
Autoimmune destruction of pancreatic beta-cells leading to absolute deficiency of insulin production

DM[2]

Type 2 DM (T2DM)
Relative deficiency of insulin secretion in response to insulin resistance to peripheral tissues

Risk factors for DM[2]

Genetic
• Ethnicity
• Family history/genetic predisposition
• Population ageing

Metabolic
• Metabolic memory/epigenetics
• Gut dysbiosis

Environmental
• Sedentary lifestyle
• Obesity
• Unhealthy diet

Ethnic differences in DM
DM is a polygenic disease with multiple susceptibility loci and its prevalence varies with ethnicity and geographical region[2]
• Higher risk in Japanese, Hispanic, and Native American people
• Higher incidence rates in Asians compared with the White population in the United Kingdom and United States
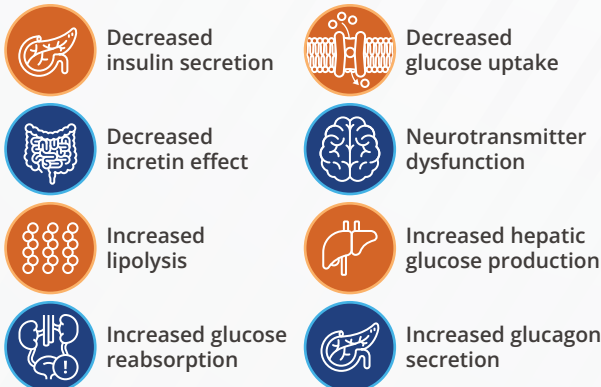
Prevalence of DM among ethnic groups in the United States of America[3]

17.4% South Asians

13% Non-Hispanic Black

10.2% Hispanic Latinos

7.8% Non-Hispanic White

Understanding DM pathophysiology is critical for its effective prevention and management

Pathophysiology of DM[4]

Eight core pathophysiological mechanisms, known as "Ominous octet," contribute to the development of T2DM

Decreased insulin secretion

Decreased glucose uptake

Decreased incretin effect

Neurotransmitter dysfunction

Increased lipolysis

Increased hepatic glucose production

Increased glucose reabsorption

Increased glucagon secretion

Accordingly, anti-diabetic therapeutics are developed to target these core defects

Prediabetes

Glucose dysregulation that does not meet the diagnostic criteria for T2DM is categorised as prediabetic, and untreated prediabetes can develop into T2DM[5]

Incidences of prediabetes and T2DM are increasing globally[5]

Prediabetes — Obesity

Waist circumference, not body mass index, is a good indicator of prediabetes[6]

Prediabetes — Coronary artery disease

Mean platelet volume[7]
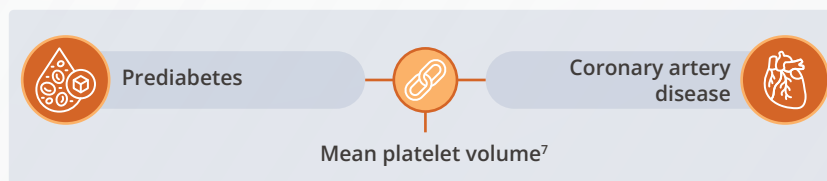
Early diagnosis and lifestyle interventions positively impact clinical outcomes and public health[6]

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Complications and comorbidities linked to DM[1,4]

Cardiovascular diseases (CVD)	Vision defects	Chronic inflammation
Kidney failure	Dyslipidaemia and atherosclerosis	Diabetic foot ulcers

Prolonged hyperglycaemia can cause serious disabilities, including lower limb amputation, reducing patients' quality of life[4]

Red blood cell (RBC) defects in DM[8]

Prevalence of anaemia in patients with diabetes: 14%–45%[8]
In chronic hyperglycaemia, RBCs display morphological, enzymatic, and biophysical changes, leading to phagocytic clearance[8]

Cardiometabolic multimorbidity

Co-occurrence of ≥1 cardiometabolic diseases with overlapping risk factors, aetiology, and bidirectional interactions[9,10]

Prevalence is higher in male, older, non-Hispanic Black people[9]

7.5% Hypertension and diabetes

2.2% Hypertension, diabetes, and coronary heart disease (CHD)

1.8% Hypertension and CHD

From 1999 to 2018
Higher prevalence of cardiometabolic multimorbidity among both genders of non-Hispanic White people[9]

Virus- or immunotherapy-induced DM

Severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2)-induced DM[11,12]

SARS-CoV-2 infection, the cause of coronavirus disease 2019 (COVID-19), damages multiple organs due to systemic inflammatory response and induces new-onset diabetes[11]
• Pancreatic β-cell destruction
• Tumour necrosis factor-induced insulin resistance in the skeletal muscle and adipose tissue
• Sustained hyperglycaemia due to hepatic gluconeogenesis

Regular screening of diabetes and prediabetes is advocated for high-risk populations with a history of SARS-CoV-2 infection[12]

Frequent blood glucose monitoring and personalised adjustment of medications are required	**Clinical guidelines for the management of DM[12]**	Both healthcare providers and their patients should adhere to COVID-19-related precautions
Patients should strictly adhere to prescribed medications, such as insulin injections		Healthcare providers should strongly encourage healthy food intake and physical activity in patients with DM

If blood glucose levels are consistently higher than usual, patients should consult their physician immediately

Disease management in patients with DM and COVID-19[12]

• Insulin and dipeptidyl peptidase 4 (DPP4) inhibitors • Metformin and sodium–glucose cotransporter 2 (SGLT2) inhibitors

Immune-related DM (irDM)

• Hyperglycaemic disorders associated with the use of immune checkpoint inhibitors (ICPis) are referred to as irDM[13]
• ICPis such as anti-programmed cell death 1 (PD-1) and anti-PD ligand 1 monoclonal antibody[13]

Pathophysiology of irDM[13]

• ICPi-induced pancreatic islet autoimmunity in genetically predisposed patients
• Altered gut microbiome
• Involvement of exocrine pancreas
• Immune-related acquired generalised lipodystrophy

Guidelines for the management of irDM[13]

• Patients' education for the recognition of initial symptoms of irDM
• Oral therapy or add-on insulin
• Regular endocrinology/diabetology consultation
• Glycated haemoglobin (HbA1c) target: <10.0%
• Withholding ICPi for severe irDM until glucose control

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Advanced, computational systems biology approaches help identify newer therapeutic targets

Novel network modelling approach[14]

Models that capture the dynamics of glucose[14]	**Glucose-insulin ordinary differential equation model** • Predicts over very short time periods • Used to study the effect of insulin injection on the liver	**Constraint-based modelling** • Assumes steady state to predict over the long term • Used to study the effects of hyperglycaemia over decades
Models that integrate different datatypes[14]	**Gene regulatory network analysis** • Analyse transcription factors linked to stress response in T2DM	**Co-expression Bayesian network study** • Cell-specific gene networks and driver genes linked to insulin sensitivity/resistance
Models to evaluate the role of gut microbiome[14]	**Multi-organ network study** • Insulin resistance in white adipose tissues • Species of gut microbiota associated with high fat/high sugar diet	**Community model** • Metformin treatment altered the composition of the gut microbiome • Increase in bacteria expressing pectin- and mannose-degrading enzymes

Clinical management of DM[1,15]

Standards of Medical Care in Diabetes by the American Diabetes Association (ADA)

Lifestyle management[15]

Consumption of healthy diet (avoid sugar and saturated fat)	Avoidance of tobacco	Maintenance of healthy body weight	Regular physical activity	Adequate sleep

Metformin monotherapy[15]

If the HbA1c target is not achieved following treatment, insulin administration or a different combination of drugs is considered[15]

Other Food and Drug Administration-approved anti-diabetic agents[1,15]

Sulfonylureas	α-glucosidase inhibitors	SGLT2 inhibitors	DPP-4 inhibitors
Thiazolidinediones	Meglitinides (glinides)	Glucagon-like peptide-1 receptor agonists	

Therapy is chosen depending on the efficacy, cost, potential side effects, and patient preferences[1,15]

In individuals with obesity and diabetes, semaglutide is recommended[16]

For patients with chronic T2DM and established atherosclerotic CVD, ADA recommends newer glucose-lowering agents, such as empagliflozin or liraglutide[15]

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- DM is increasingly prevalent in low- and middle-income countries where healthcare needs remain unmet, especially among women and rural residents who have higher rates of hospitalisations and mortality[17]

- Novel therapeutic agents that minimise chronic complications of diabetes such as retinopathy or neuropathy, and which have limited gastrointestinal side effects, hypoglycaemic risk, weight gain, and fracture risk are desirable[18,19]

- Anti-diabetic drugs customised to suit the metabolic differences arising from genetic variations across various ethnicities are foreseen[19]

A multidisciplinary clinical care team that includes endocrinologists, oncologists, urologists, ophthalmologists, and cardiologists is critical for the optimal management of diabetes and its comorbidities[13]

Recommendations for optimal care[13]

- Improve disease screening and frequent monitoring for complications
- Improve care and communication within the multidisciplinary team
- Increase patient awareness and adherence to therapy
- Educate to mobilise communities and garner support

Key messages

- ✔ **Lifestyle management with a healthy diet, increased physical activity, and regular disease monitoring can significantly delay the onset of DM**

- ✔ **Multidisciplinary clinical care that covers comprehensive management of hyperglycaemia along with associated comorbidities is the recommended treatment approach**

- ✔ **To reduce diabetes-related complications, disabilities, hospitalisation, and mortality rates, it is essential to support vulnerable patients with diabetes experiencing unmet healthcare needs**

- ✔ **To improve adherence to therapy and follow-up, patient awareness and education must be facilitated**

Take-home message

❝ **Understanding the complexities of diabetes, prioritising lifestyle modifications, ensuring coordinated care, recognising the impacts of COVID-19, and developing tailored treatments are essential for improving management and outcomes for patients with diabetes** ❞

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