MEDICAL EDUCATION SYSTEMS INC

DIABETES- TRENDS AND UPDATES

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DIABETES- TRENDS AND UPDATES

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Learning Objectives

1. **Understand the Basic Concepts of Diabetes:**
    - Define diabetes and describe its primary characteristic of elevated blood glucose levels.
    - Differentiate between the main types of diabetes: Type 1, Type 2, Gestational Diabetes, LADA, and MODY.
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2. **Identify and Explain the Pathophysiology of Each Type of Diabetes:**
    - Explain the autoimmune nature of Type 1 diabetes and its impact on insulin production.
    - Describe the mechanisms of insulin resistance and impaired insulin production in Type 2 diabetes.
    - Understand the temporary nature of gestational diabetes and its hormonal causes.
    - Discuss the characteristics of LADA and its overlap with both Type 1 and Type 2 diabetes.
    - Explain the genetic basis and clinical presentation of MODY.

3. **Recognize Risk Factors and Epidemiological Trends:**
    - Identify key risk factors for developing diabetes, including genetic, lifestyle, and socioeconomic factors.
    - Analyze global trends in diabetes prevalence and understand the differences in prevalence between urban and rural areas.

4. **Diagnose and Manage Diabetes:**
    - Understand the diagnostic criteria and methods for each type of diabetes, including blood glucose testing and emerging technologies.
    - Discuss current and emerging treatment options, including lifestyle interventions, medications, and technological advancements.

5. **Appreciate the Public Health Implications of Diabetes:**
    - Understand the significance of monitoring and understanding diabetes trends for public health planning.
    - Discuss the challenges in managing diabetes at the population level and strategies for improving treatment outcomes and prevention efforts.

6. **Apply Knowledge to Clinical and Public Health Contexts:**
    - Utilize knowledge of diabetes types, risk factors, and treatments in clinical decision-making and patient education.
    - Advocate for and implement strategies for diabetes prevention and management within communities and healthcare settings

Chapter 1 Introduction to Diabetes

Diabetes

Diabetes is a medical issue that alters the body's glucose utilization. The full name of diabetes is Diabetes Mellitus-Mellitus, is a Latin word that means "Sweet as Honey". In a healthy body, whenever you eat food, after being broken down and absorbed, causes a rise in the glucose (sugar levels). After this, the pancreas secretes a hormone called insulin to reduce the sugar levels in the bloodstream. Diabetes mellitus, commonly referred to as diabetes, is a group of metabolic disorders characterized by high blood glucose levels over a prolonged period. If an individual is diabetic, they are either not producing enough insulin or the existing insulin is not practical. If that is the case too much sugar stays in the blood causing symptoms and complications of diabetes. There are several types of diabetes. Everyone who suffers from diabetes has a heightened blood sugar concentration (hyperglycemia).

However, the causes of this elevation and the methods of treating it may differ, depending on the kind of diabetes. There are different types of diabetes.

Type 1 diabetes

Type 2 diabetes

Gestational diabetes

LADA diabetes (Latent Autoimmune Diabetes in Adults)

MODY diabetes (Maturity Onset Diabetes of the Young)

TYPE 1 Diabetes

Type 1 diabetes accounts for about 10% of all types of diabetes. It used to be called insulin-dependent diabetes or juvenile diabetes due to its development mechanism and the age at which the disease is most often diagnosed. The onset of the illness usually falls between the ages of 10 and 14. Type 1 diabetes is caused by the almost absolute destruction of the pancreas's insulin-producing cells (so-called beta cells). The immune system starts manufacturing antibodies that start destroying pancreas cells for an unexplained cause. Damaged cells can no longer produce insulin, leading to sugar accumulation in the bloodstream.
Primary symptoms of type 1 diabetes are usually very characteristic and severe, which result from very high blood sugar levels.
Type 1 diabetes is not inherited, but people with type 1 diabetes are genetically predisposed to other autoimmune diseases. There are no treatments that can prevent type 1 diabetes.

Type 2 Diabetes

Type 2 diabetes is also known as non -insulin- dependent or adult -onset diabetes. The most prevalent form of diabetes is type 2 diabetes. Experts estimate that around one in ten adults has type 2 diabetes. Type 2 diabetes has two main causes: reduced insulin production, which is caused on by a number of genetic factors and body cells becoming resistant to the impact of insulin, which can be driven on by both genetic and environmental (such as obesity) factors.

At the time of diagnosis, the pancreas of persons with type 2 diabetes typically makes insulin. However, either there isn't enough of it to maintain the correct blood sugar level, or the insulin is ineffective due to a condition known as insulin resistance. Insulin resistance is the reduced sensitivity of body tissues to the action of insulin.

Because in this type of diabetes, the problem is not a lack of insulin but its malfunction, the symptoms of the disease are mild and often do not occur at first. Type 2 diabetes is usually determined when a person has higher than normal glucose levels which can commonly be found out by chance when someone undergoes screening. However, this does not mean that it is a less severe disease. If left untreated, long-term injury to the body can occur even though signs and symptoms may not initially be present.

Gestational Diabetes

Gestational diabetes is a particular type of diabetes. It occurs in about 10% of pregnancies
During pregnancy, there is an increase in the concentration of certain hormones (estrogens, progesterone, placental lactogen, and prolactin). These hormones act as insulin antagonists, blocking insulin action on tissues and decreasing body cells' sensitivity to insulin. Hence the rise in blood glucose.
Gestational diabetes is when blood glucose levels remain elevated during pregnancy. It appears only in women that were not diagnosed with diabetes before pregnancy. This disorder resolves after delivery.
Symptoms of gestational diabetes usually do not appear. Laboratory tests are the only way to identify high glucose levels in the blood. For this reason, it is absolutely essential for every pregnant woman to go for regular check-ups.

An oral glucose tolerance test is used to diagnose gestational diabetes. It should be taken while fasting and is composed of several stages. The first step is a blood test for fasting glucose. Then the pregnant woman must drink a solution containing 75 grams of glucose.
The woman is requested to rest seated and return for a blood draw after 60 and 120 minutes. This medical procedure is carried out on females between 24- and 28-weeks' gestation. However, a physician can request this examination sooner if the woman is at an increased danger of getting diabetes.
Gestational diabetes goes away after delivery.

It is worth noting, however, that pregnant women who have had gestational diabetes are at risk of developing it in the future. Sometimes, blood sugar amounts do not go back to their usual levels after the birth of a baby. This does not mean that the mother had gestational diabetes, but that regular diabetes was found out unexpectedly during her pregnancy. In such a situation, it is necessary to continue treatment for life.

LADA Diabetes (Latent Autoimmune Diabetes in Adults)

LADA is a specific type of type 1 diabetes that occurs when the immune system attacks the insulin-producing pancreas cells. The immune system creates antibodies which target pancreatic cells and cause their destruction. Unlike type 1 diabetes, where symptoms appear suddenly, LADA diabetes develops over the years, and blood glucose levels rise gradually. It can occur at any age but generally between ages 30 – 70. Patients with LADA type diabetes are average or slightly overweight, do not have a family history of diabetes, but often suffer from another autoimmune disease (hyperthyroidism or hypothyroidism, celiac disease).

MODY Diabetes (Maturity Onset Diabetes of the Young)

MODY diabetes, or Maturity Onset Diabetes of the Young, is a rare type of diabetes (about 2% of all cases) that is caused by an inherited gene mutation. It occurs at a young age, which is typical of type 1 diabetes, while the course of the disease is similar to type 2 diabetes. No connection exists between this specific kind of diabetes and being overweight or obese.

Symptoms

Symptoms of diabetes may occur suddenly. In type 2 diabetes, the symptoms can be mild and may take many years to be noticed.

Symptoms of diabetes include:

- feeling very thirsty
- needing to urinate more often than usual
- blurred vision
- feeling tired
- losing weight unintentionally

Over time, diabetes can damage blood vessels in the heart, eyes, kidneys and nerves.

People with diabetes have a higher risk of health problems including heart attack, stroke and kidney failure.

Diabetes can cause permanent vision loss by damaging blood vessels in the eyes.

Many people with diabetes develop problems with their feet from nerve damage and poor blood flow. This can cause foot ulcers and may lead to amputation.

Historical Overview of Diabetes

Over 3,000 years ago, the ancient Egyptians mentioned a condition that appears to have been type 1 diabetes. It featured excessive urination, thirst, and weight loss. In ancient India, people discovered that they could use ants to test for diabetes by presenting urine to them. If the ants came to the urine, this was a sign that it contained high sugar levels. They called the condition madhumeha, meaning honey urine. During the third century B.C.E., Apollonius of Memphis mentioned the term “diabetes,” which may have been its earliest reference. In time, Greek physicians also distinguished between diabetes mellitus and diabetes insipidus.

Diabetes insipidus has no link with diabetes mellitus. While it also leads to thirst and urination, it does not affect the body's production or use of insulin. Diabetes insipidus results from a problem with a hormone called vasopressin that the pituitary gland produces. The ancient Roman doctor Galen mentioned diabetes but noted that he had only ever seen two people with it, which suggests that it was relatively rare in those days. By the fifth century C.E., people in India and China had worked out that there was a difference between type 1 and type 2 diabetes. They noted that type 2 diabetes was more common in heavy, wealthy people than in other people. At that time, this might have implied that these individuals ate more than other people and were less active.

Nowadays, the ready supply of processed food has weakened the association between wealth and eating more, but obesity, diet, and a lack of exercise are still risk factors for type 2 diabetes. The term diabetes mellitus comes from the Greek word "diabetes" (to siphon or pass through) and the Latin word "mellitus" (honey or sweet).

In the Middle Ages, people believed that diabetes was a disease of the kidneys, but an English doctor in the late 18th century found that it occurred in people who had experienced an injury to the pancreas. In 1776, Matthew Dobson confirmed that the urine of people with diabetes could have a sweet taste. According to an article that the journal *Medical Observations and Enquiries* published, he measured the glucose in urine and found that it was high in people with diabetes.

Dobson also noted that diabetes could be fatal in some people but chronic in others, further clarifying the differences between type 1 and type 2. By the early 19th century, there were no statistics about how common diabetes was, there was no effective treatment, and people usually died within weeks to months of first showing symptoms.

Importance of Studying Trends in Diabetes

Understanding trends and research is essential for advancing our understanding of the disease, developing innovative and effective treatments, improving treatment options, preventing complications, enhancing the lives of individuals affected by diabetes and ultimately finding a cure.

Over the past few decades, the prevalence of diabetes has increased significantly. According to the International Diabetes Federation (IDF), the number of adults living with diabetes has more than tripled in the past 20 years. Key trends include:

- **Increasing Prevalence:** The global prevalence of diabetes in adults has risen from 4.7% in 1980 to 9.3% in 2019.

- **Geographic Variations:** The highest prevalence rates are found in the Middle East, North Africa, and South-East Asia. Low- and middle-income countries are experiencing the most rapid increases.

- **Age Distribution:** While diabetes traditionally affected older adults, there is a growing prevalence among younger age groups, including children and adolescents.

Chapter 2 Epidemiology of Diabetes

Global Prevalence and Incidence Rates

Understanding the global prevalence and incidence rates of diabetes is essential for public health planning and resource allocation. Epidemiological data provides insights into the scale of the diabetes epidemic and helps identify populations at higher risk.

Global Prevalence

The global prevalence of diabetes has been rising steadily. According to the IDF Diabetes Atlas 9th Edition (2019)

In 2014, 8.5% of adults aged 18 years and older had diabetes. In 2019, diabetes was the direct cause of 1.5 million deaths and 48% of all deaths due to diabetes occurred before the age of 70 years. Another 460 000 kidney disease deaths were caused by diabetes, and raised blood glucose causes around 20% of cardiovascular deaths *(1)*.

Between 2000 and 2019, there was a 3% increase in age-standardized mortality rates from diabetes. In lower-middle-income countries, the mortality rate due to diabetes increased 13%.

By contrast, the probability of dying from any one of the four main noncommunicable diseases (cardiovascular diseases, cancer, chronic respiratory diseases or diabetes) between the ages of 30 and 70 decreased by 22% globally between 2000 and 2019.

- Approximately 463 million adults (20-79 years) were living with diabetes in 2019. This number is expected to rise to 700 million by 2045.
- The global prevalence of diabetes was estimated at 9.3% in 2019 and is projected to increase to 10.9% by 2045.
- The regions with the highest prevalence rates include the Middle East and North Africa (12.2%), South-East Asia (11.4%), and Western Pacific (11.0%).

Incidence Rates

- **Prevalence:**
- In 2021, 38.4 million Americans, or 11.6% of the population, had diabetes.

2 million Americans have type 1 diabetes, including about 304,000 children and adolescents

- **Diagnosed and undiagnosed:** Of the 38.4 million adults with diabetes, 29.7 million were diagnosed, and 8.7 million were undiagnosed.
- **Prevalence in seniors:** The percentage of Americans age 65 and older remains high, at 29.2%, or 16.5 million seniors (diagnosed and undiagnosed).
- **New cases:** 1.2 million Americans are diagnosed with diabetes every year.
- **Prediabetes:** In 2021, 97.6 million Americans age 18 and older had prediabetes.

Diabetes in youth

- About 352,000 Americans under age 20 are estimated to have diagnosed diabetes, approximately 0.35% of that population.
- In 2017–2018, the annual incidence of diagnosed diabetes in youth was estimated at 18,200 with type 1 diabetes, 5,300 with type 2 diabetes.

Diabetes by race/ethnicity

The rates of diagnosed diabetes in adults by race/ethnic background are:

- 13.6% of American Indians/Alaskan Native adults
- 12.1% of non-Hispanic Black adults
- 11.7% of Hispanic adults
- 9.1% of Asian American adults
- 6.9% of non-Hispanic White adults

The breakdown among Asian American adults:

- 12.2% of Filipino
- 10.8% of Asian Indian
- Chinese, Japanese, Korean, and Vietnamese prevalences range from 6.1-7.1%
- 8.9% of other Asian American groups

The breakdown among Hispanic adults:

- 13.3% Puerto Rican
- 11.1% Mexican or Mexican American
- 9.4% Dominican
- 9.0% Cuban
- Central American, South American, and other Hispanic, Latino, or Spanish adults had prevalences ranging from 5.0%-7.3%

Deaths

Diabetes was the eighth leading cause of death in the United States in 2021 based on the 103,294 death certificates in which diabetes was listed as the underlying cause of death. In 2021, diabetes was mentioned as a cause of death in a total of 399,401 certificates.

Cost of diabetes

Updated November 2, 2023

$412.9 billion: Total cost of diagnosed diabetes in the United States in 2022

$306.6 billion was for direct medical costs

$106.3 billion was in indirect costs

After adjusting for population age and sex differences, average medical expenditures among people with diagnosed diabetes were 2.6 times higher than what expenditures would be in the absence of diabetes.

Geographic Distribution

Geographic variations in diabetes prevalence and incidence highlight the influence of environmental, lifestyle, and socioeconomic factors.

- **Urban vs. Rural:** Diabetes prevalence is generally higher in urban areas compared to rural areas. Urbanization is associated with lifestyle changes such as reduced physical activity and increased consumption of processed foods, contributing to higher diabetes rates.

  During 1999–2018, the proportion of U.S. adults with diabetes residing in rural areas ranged between 15% and 19.5%. In 1999–2006, there were not statistically significant rural-urban differences in poor ABCS. However, from 1999–2006 to 2013–2018, there were greater improvements for urban adults with diabetes than for rural for BP ≥140/90 mmHg (relative odds ratio [OR] 0.8, 95% CI 0.6–0.9) and non-HDL ≥160 mg/dL (≥4.1 mmol/L) (relative OR 0.45, 0.4–0.5). These differences remained statistically significant after adjustment for race/ethnicity, education, poverty levels, and clinical characteristics. Yet, over the 1999–2018-time, minority race/ethnicity, lower education attainment, poverty, and lack of health insurance coverage were factors associated with poorer A, B, C, or S in urban adults compared with their rural counterparts.

  Over two decades, rural U.S. adults with diabetes have had less improvement in BP and cholesterol control. In addition, rural-urban differences exist across sociodemographic groups, suggesting that efforts to narrow this divide may need to address both socioeconomic and clinical aspects of care.

  Rural-urban disparities have been described for a wide variety of illnesses and mortality rates. Since 1999, rural residents generally have had higher age-adjusted mortality rates, including for the five leading causes of death (heart disease, stroke, cancer, unintentional injury, and chronic lower respiratory disease). Although national mortality rates have generally declined in the past few decades, the urban-rural disparity in life expectancy has widened, with greater improvements in urban areas than rural. Many rural communities experience greater prevalence of chronic health conditions and complications and less access to comprehensive health care.

Diabetes complications, such as microvascular (nephropathy, neuropathy, and retinopathy) and macrovascular diseases (atherosclerosis of coronary, cerebrovascular, and peripheral vasculatures) increase morbidity, disability, and mortality. As such, poor glycemic control and cardiovascular health are culprits in increasing risk for complications, declining quality of life, and greater financial burden. This has led the American Diabetes Association and other organizations to emphasize clinical care guidelines and health care quality metrics for more than three decades.

The optimal levels of some of the ABCS (A1C, blood pressure [BP], cholesterol, and smoking), key risk factors for the development of diabetes complications, have evolved over time. The most recent evolution of these guidelines is as follows: A1C <7.0% <53 mmol/mol); BP <140/90 mmHg; the lower the non-HDL cholesterol levels, the better; and avoidance of cigarette and other tobacco product or e-cigarette use. Previous analyses have documented substantial improvements in the management of ABCS until 2010 with stagnation thereafter. Disparities by age, race/ethnicity, and socioeconomic status have also persisted. Furthermore, after a 20-year decline, recent national increases in selected diabetes-related complications, particularly in young and middle-aged adults, emphasize the importance of improving poor ABCS measures and addressing disparities.

Rural areas have higher age-adjusted prevalence of diabetes than urban areas, and adults with diagnosed diabetes in rural areas report less adherence to some preventive measures, such as dilated eye or foot examinations, and more complications, such as diabetic retinopathy and foot sores, than their urban counterparts. However, there have been no comparisons of ABCS management among adults with diabetes in rural and urban areas. Since the definition of optimal ABCS control has changed over time and currently varies based on life expectancy or the presence of comorbid conditions, in this report, we assessed trends in poor ABCS among adults with diagnosed diabetes and disparities between rural and urban areas using updated national data from 1999 to 2018.

The National Health and Nutrition Examination Survey (NHANES) was designed to investigate the health and nutritional status of the noninstitutionalized U.S. civilian population through a complex multistage sampling design. Since 1999, NHANES has been conducted continuously with administration of questionnaires to obtain sociodemographic and health information (e.g., diabetes and smoking status), collection of blood samples for laboratory tests (e.g., glycohemoglobin and lipid profiles), and physical exams including measures of BP and anthropometry (e.g., BMI). Data is released in 2-year cycles.

The National Center for Health Statistics (NCHS) of the Centers for Disease Control and Prevention administers NHANES, and its Research Ethics Review Board approved the NHANES protocol. Data used in this study are publicly available

(https://wwwn.cdc.gov/nchs/nhanes/default.aspx) with the exception of urban/rural residential status, true sampling stratum, and true probability sampling unit, which were analyzed at the restricted-access NCHS Research Data Center (https://www.cdc.gov/rdc/). NHANES publicly releases pseudo sampling strata and pseudoprobability sampling unit information to minimize disclosure risk.

NHANES urban/rural residential status, used in this study, is determined in partnership with the U.S. Department of Housing and Urban Development, which geocodes addresses of NHANES participants to the 2010 census (https://wwwn.cdc.gov/Nchs/Nhanes/limited_access/GEO_2000.htm#UR). Census tracts with at least 2,500 people were considered "urban," including both urban clusters (2,500–<50,000 people) and urban areas (≥50,000 people).

All areas not included within the urban definition were considered "rural." For the proportion of county residence in an urban census tract based on 2010 census. Since rural/urban status was missing for almost 10% of participants in NHANES 1999–2018, we used multiple imputation to estimate rural/urban status for missing values including the following covariates: true sampling stratum and primary sampling unit, age, sex, and race/ethnicity.

We identified the study population using NHANES data from ten 2-year cycles (from 1999–2000 to 2017–2018). Eligibility criteria included the following: having a physical exam at the Mobile Examination Center, age ≥18 years, and responding "yes" to the question, "Other than during pregnancy, have you ever been told by a health professional that you have diabetes or sugar diabetes?" Of the 6,393 adults with diagnosed diabetes, 21 pregnant women were excluded from the analysis for a total sample size of 6,372. For this study, we grouped survey cycles into three time periods: 1999–2006 (n = 1,897), 2007–2012 (n = 2,121), and 2013–2018 (n = 2,354). We also stratified by rural (n = 872) and urban (n = 5,500) residence.

Considering the evolving clinical guidelines from both the American Diabetes Association and the American Heart Association during 1999–2018, for the purpose of this study, we focused on poor ABCS measures. Poor ABCS measures were defined as values above cut points based on which patients with diabetes with or without comorbidities would be universally considered to have poor control, as diagnosis criteria, or threshold for treatment initiation during this time period.

For this study, poor ABCS was A1C >9.0% (>75 mmol/mol), BP ≥140/90 mmHg (systolic BP ≥140 mmHg or diastolic BP ≥90 mmHg), non-HDL cholesterol ≥160 mg/dL (≥4.1 mmol/L) (equivalent to LDL ≥130 mg/dL, ≥3.4 mmol/L), and being a current smoker. Non-HDL cholesterol was calculated by subtracting values for HDL cholesterol from total cholesterol. Participants were considered current smokers if they 1) self-reported smoking at least 100 cigarettes in their life and now smoking cigarettes every day or some days or 2) had serum cotinine levels >10 ng/mL.

We described characteristics and demographics of adults with diagnosed diabetes across three time periods (1999–2006, 2007–2012, and 2013–2018) and by rural/urban residence as percentages and tested differences in distributions across time periods or rural/urban residence using a design-based Pearson χ^2 test. The demographics considered were age-group (18–44, 45–64, and ≥65 years), sex, and race/ethnicity (non-Hispanic White, non-Hispanic Black, Mexican American, and other race/multiracial). Other characteristics included socioeconomic variables, such as education attainment (less than high school diploma, high school diploma, some college, and college degree) and poverty-to-income ratio (PIR) (<100%, 100–299%, 300–499%, and ≥500%).

Medical or clinical characteristics were also included (health insurance coverage [yes/no], time since diabetes diagnosis [0 to <5, 5 to <15, and ≥15 years], age at diabetes diagnosis [<30, 30 to <45, 45 to <60, and ≥60 years], and BMI [<25.0, 25.0–29.9, and ≥30 kg/m^2]).

Differences between rural and urban residence in the distribution of ABCS categories were assessed—ranging from A1C <6.0% to ≥10.0% (<42 to ≥86 mmol/mol), BP <120/80 to ≥160/100 mmHg, non-HDL cholesterol <130 to ≥220 mg/dL (<3.4 to ≥5.7 mmol/L), and smoking status of never, former, and current smoker—with a design-based Pearson χ^2 test. We used weighted logistic regression models accounting for survey design to examine the relationship between rural/urban residence and poor ABCS. For each of the ABCS, a model was used with the poor ABCS measure as the dependent variable. For odds ratio (OR) estimates between rural and urban residence at each time period and changes over time, the regression model contained a two-way interaction for rural/urban residence * time period, including lower-order variables and covariates. Independent variables included as covariates in the model were analyzed in a staged approach beginning with model 1, which was unadjusted (no covariates). Model 2 included demographic covariates (age [years], sex, race/ethnicity). The covariates included in model 3 were socioeconomic factors (education attainment and PIR [%]).

Model 4 adjusted for clinical characteristics such as BMI (kg/m^2), age at diabetes diagnosis (years), and years since diabetes diagnosis. Model 5 was the full model and included all covariates from models 2–4. Linear combinations (STATA lincom command) of estimated parameters were used to estimate adjusted ORs for each time period and relative ORs between time periods (1999–2006 vs. 2013–2018 and 2007–2012 vs. 2013–2018) to assess changes over time.

For examining sociodemographic and clinical characteristics and disparities in poor ABCS between rural and urban residence, the regression model contained a two-way interaction for rural/urban residence * characteristics lower-order variables with.

Linear combinations of estimated parameters were used to estimate ORs between rural and urban residence for each sociodemographic and clinical characteristics subgroup. Sociodemographic and clinical characteristics considered were age, sex, race/ethnicity, education attainment, PIR, health insurance coverage, time since diabetes diagnosis, age at diabetes diagnosis, and BMI.

Results with *P* values <0.05 were determined to be statistically significant. We performed all analyses using STATA 14.0 accounting for the NHANES complex sampling design. Examination sample weights were used for all analyses.

Characteristics of U.S. adults with diagnosed diabetes significantly changed across time periods (Table 1). The population of adults with diagnosed diabetes shifted toward older ages (mean age changed from 58.8 to 60.5 years, $P = 0.01$), more men (from 47.7% to 53.1%, $P = 0.024$), higher education attainment (some college, from 26.9% to 33.7%, and college degree or more, from 14.9% to 21.4%; $P < 0.001$), and higher PIR (mean, from 2.6 to 2.8; $P = 0.039$). There were also changes in having health insurance coverage (from 89.6% to 91.9%; $P = 0.003$), longer duration of diabetes since diagnosis (≥15 years, from 26.1% to 32.3%; $P < 0.001$), and greater BMI (mean, from 32.1 to 33.0 kg/m^2; $P = 0.014$). However, the race/ethnicity and rural/urban distributions did not statistically significantly differ across the time periods.

Table 1—

Characteristics of U.S. adults with diagnosed diabetes: NHANES 1999–2018

	1999–2006 (*n* = 1,897)	2007–2012 (*n* = 2,121)	2013–2018 (*n* = 2,354)	Year groups *P* value*	Rural (*n* = 872)	Urban (*n* = 5,500)	Rural vs urban *P* value†
Age (years)	58.8 (0.5)	60.0 (0.4)	60.5 (0.4)	0.010	61.3 (0.6)	59.5 (0.3)	0.010
Women	52.3	51.0	46.9	0.024	48.0	50.1	0.353
Race/ethnic group							
Non-Hispanic White	62.6	60.5	60.5	0.332	83.1	56.2	<0.001
Non-Hispanic Black	16.6	17.7	13.5		6.9	17.7	
Mexican American	7.4	8.3	10.2		4.0	9.9	
Other	13.4	13.5	15.8		6.1	16.2	
Education (among those aged ≥25 years)							
<High school diploma	32.1	29.5	19.9	<0.001	24.2	27.0	0.007
High school diploma	26.0	24.5	25.1		31.0	23.9	
Some college	26.9	27.9	33.7		30.6	29.8	
≥College degree	14.9	18.1	21.4		14.2	19.4	
PIR	2.6 (0.1)	2.6 (0.1)	2.8 (0.1)	0.039	2.8 (0.1)	2.6 (0.1)	0.051
Health insurance coverage	89.6	87.9	91.9	0.003	91.0	89.8	0.394
Time since diabetes diagnosis (years)							
0 to <5	35.2	33.2	27.5	<0.001	31.5	31.5	0.983
5 to <15	38.7	38.8	40.2		39.7	39.3	
≥15	26.1	28.0	32.3		28.9	29.2	
BMI (kg/m^2)	32.1 (0.3)	33.0 (0.3)	33.0 (0.3)	0.014	33.8 (0.4)	32.5 (0.2)	0.001
Residential status							

Rural	15.0	19.9	19.5	0.414	—	—
Urban	85.0	80.1	80.5		—	—

Data are % or means (SE).

*Design-based Pearson χ^2 test of characteristic by year groups.

†Design-based Pearson χ^2 test of characteristic by rural/urban area.

Over 1999–2018, adults with diagnosed diabetes that reside in urban areas were more likely to be younger (mean age 59.5 years for urban and 61.3 years for rural, P = 0.010), a lower proportion were non-Hispanic White (56.2% urban and 83.1% rural, $P < 0.001$), there was a higher proportion of education attainment at the extremes (<high school, 27.0% urban and 24.2% rural; college degree or higher, 19.4% urban, and 14.2% rural; $P = 0.007$), and individuals in urban areas on average had lower BMI than those in rural areas (mean 32.5 kg/m^2 urban and 33.8 kg/m^2 rural; $P = 0.001$). There was no significant difference in sex, PIR, health insurance coverage, or time since diabetes diagnosis between rural and urban residence of adults with diagnosed diabetes.

In 1999–2006 (1st time period), there were no significant associations between rural/urban residence and each poor ABCS measure (models 1–5) (Table 2). Adults with diagnosed diabetes residing in urban areas were less likely to have non-HDL cholesterol ≥160 mg/dL (≥4.1 mmol/L) compared with those in rural areas (unadjusted OR 0.7, 95% CI 0.4–0.9) in 2007–2012 (2nd time period) and in 2013–2018 (3rd time period) (unadjusted OR 0.5, 0.3–0.8). There were significant differences between the 1st and 3rd time periods in the OR for BP ≥140/90 mmHg (relative OR 0.8, 0.6–0.9) and non-HDL cholesterol ≥160 mg/dL (≥4.1 mmol/L) (relative OR 0.45, 0.4–0.5). These significant differences from the 1st and 3rd time periods signify that rural residents were more likely than urban residents to have poor BP and poor cholesterol by 2013–2018, which persisted even after adjustment for socioeconomic, demographic, and clinical measures. There were no statistically significant associations of rural/urban residence with current smoking status or A1C >9.0% (>75 mmol/mol) in adults with diagnosed diabetes at any time period or over time.

Table 2—

Trends in ORs of poor ABCS for urban versus rural residence in U.S. adults aged ≥18 years with diagnosed diabetes: NHANES, 1999–2018

Urban vs. rural: reference	**1999–2006**	**2007–2012**	**2013–2018**	**Relative OR 1999–2006 and 2013–2018**	**Relative OR 2007–2012 and 2013–2018**
Model 1, unadjusted					

A1C >9.0% (>75 mmol/mol)	1.8 (0.8–4.0)	1.6 (0.7–3.5)	1.4 (0.7–3.2)	0.8 (0.6–1.0)	0.9 (0.7–1.2)
BP ≥140/90 mmHg	1.0 (0.7–1.5)	0.8 (0.5–1.1)	0.8 (0.6–1.2)	0.8 (0.6–0.9)	1.1 (0.9–1.4)
Non-HDL cholesterol ≥160 mg/dL (≥4.1 mmol/L)	1.1 (0.8–1.7)	0.7 (0.4–0.9)	0.5 (0.3–0.8)	0.45 (0.4–0.5)	0.8 (0.6–0.9)
Current smoker	0.8 (0.5–1.4)	0.8 (0.5–1.2)	0.7 (0.4–1.2)	0.8 (0.6–1.1)	0.9 (0.7–1.1)
Model 2 covariates: age, sex, race/ethnicity					
A1C >9.0% (>75 mmol/mol)	1.5 (0.7–3.2)	1.3 (0.6–2.7)	1.2 (0.6–2.6)	0.8 (0.6–1.0)	0.9 (0.7–1.2)
BP ≥140/90 mmHg	1.0 (0.7–1.5)	0.7 (0.5–0.9)	0.8 (0.5–1.1)	0.7 (0.6–0.9)	1.1 (0.9–1.4)
Non-HDL cholesterol ≥160 mg/dL (≥4.1 mmol/L)	1.0 (0.7–1.6)	0.6 (0.4–0.9)	0.5 (0.3–0.7)	0.5 (0.4–0.6)	0.8 (0.6–0.9)
Current smoker	0.8 (0.5–1.4)	0.8 (0.5–1.3)	0.7 (0.4–1.3)	0.9 (0.7–1.2)	0.9 (0.7–1.2)
Model 3 covariates: educationand PIR					
A1C >9.0% (>75 mmol/mol)	1.9 (0.9–3.9)	1.7 (0.8–3.4)	1.6 (0.8–3.3)	0.8 (0.6–1.1)	1.0 (0.7–1.2)
BP ≥140/90 mmHg	1.0 (0.7–1.5)	0.8 (0.5–1.1)	0.9 (0.6–1.3)	0.8 (0.6–1.0)	1.1 (0.9–1.4)
Non-HDL cholesterol ≥160 mg/dL (≥4.1 mmol/L)	1.2 (0.8–1.8)	0.7 (0.5–1.1)	0.6 (0.4–0.9)	0.5 (0.4–0.6)	0.8 (0.7–1.0)
Current smoker	0.9 (0.5–1.6)	0.9 (0.5–1.6)	0.8 (0.5–1.5)	0.9 (0.7–1.2)	0.9 (0.7–1.2)

Model 4 covariates: BMI, age at diabetes diagnosis, and years since diabetes diagnosis					
A1C >9.0% (>75 mmol/mol)	2.0 (0.9–4.3)	1.8 (0.8–3.8)	1.6 (0.7–3.5)	0.8 (0.6–1.1)	0.9 (0.7–1.2)
BP ≥140/90 mmHg	1.1 (0.8–1.5)	0.8 (0.5–1.1)	0.8 (0.6–1.1)	0.7 (0.6–0.9)	1.0 (0.8–1.3)
Non-HDL cholesterol ≥160 mg/dL (≥4.1 mmol/L)	1.1 (0.7–1.8)	0.7 (0.4–1.0)	0.5 (0.3–0.8)	0.5 (0.4–0.6)	0.8 (0.6–0.99)
Current smoker	0.8 (0.5–1.4)	0.8 (0.5–1.3)	0.7 (0.4–1.2)	0.9 (0.7–1.2)	0.9 (0.7–1.2)
Model 5 covariates: all from models 2–4					
A1C >9.0% (>75 mmol/mol)	1.9 (0.8–4.2)	1.7 (0.8–3.7)	1.6 (0.8–3.6)	0.9 (0.7–1.2)	1.0 (0.7–1.3)
BP ≥140/90 mmHg	1.1 (0.8–1.6)	0.8 (0.5–1.1)	0.8 (0.6–1.2)	0.8 (0.6–0.97)	1.1 (0.8–1.4)
Non-HDL cholesterol ≥160 mg/dL (≥4.1 mmol/L)	1.1 (0.7–1.7)	0.7 (0.4–1.0)	0.6 (0.4–0.9)	0.5 (0.4–0.6)	0.9 (0.7–1.1)
Current smoker	0.9 (0.5–1.6)	0.9 (0.5–1.5)	0.8 (0.5–1.5)	1.0 (0.7–1.3)	0.9 (0.7–1.2)

Data are OR (95% CI).

Over the entire time period from 1999 to 2018, the distribution of each ABCS measure did not statistically significantly differ between adults with diagnosed diabetes residing in urban and rural areas (Fig. 1). However, the associations between rural/urban residence and poor ABCS varied by socioeconomic and clinical characteristics (Table 3).

Adults with diagnosed diabetes in urban areas were more likely to have A1C >9.0% (>75 mmol/mol) than those in rural areas if they were non-Hispanic Black (OR 2.2, 95% CI 1.6–3.2), Mexican American (2.8, 1.9–4.1), another race or multiracial (1.9, 1.3–2.9). Similarly, A1C >9.0% (>75 mmol/mol) was more likely in adults with diabetes residing in urban than rural areas if they had less than a high school diploma (2.2, 1.2–4.0), PIR <100% (1.9, 1.1–3.4) or no health insurance coverage (3.7, 2.6–5.5) or if there was 5 to <15 years since diabetes diagnosis (2.1, 1.1–3.8).

Urban adults with diagnosed diabetes were more likely than their rural counterparts to have BP ≥140/90 mmHg if they were ≥65 years old (4.4, 2.1–9.2), if they were non-Hispanic Black (1.5, 1.1–1.9), if there was 5 to <15 years (1.5, 1.03–2.2) or ≥15 years (1.9, 1.3–2.9) since diabetes diagnosis, or if they were age ≥60 years at diabetes diagnosis (2.5, 1.2–5.2). Compared with adults with diagnosed diabetes residing in rural areas, those in urban areas were less likely to have non-HDL cholesterol ≥160 mg/dL (≥4.1 mmol/L) if they were ≥65 years old (0.4, 0.3–0.8), if they had had a college degree or higher (0.6, 0.4–0.9), or if there was ≥15 years since diabetes diagnosis (0.6, 0.4–0.95). However, adults with diagnosed diabetes residing in urban areas, as compared with those in rural areas, were more likely to have non-HDL cholesterol ≥160 mg/dL (≥4.1 mmol/L) if they were Mexican American (1.5, 1.1–2.1) or other race or multiracial (1.4, 1.0–2.1), if they had no health insurance coverage (2.2, 1.6–3.1), if they were age 30 to <45 years at diabetes diagnosis (2.6, 1.3–5.4), or if they had BMI 25–29.9 kg/m^2 (2.1, 1.1–3.7) or ≥30 kg/m^2 (2.3, 1.3–4.1).

Also, adults with diagnosed diabetes and no health insurance coverage in urban areas were more likely to be current smokers than those in rural areas (2.0, 1.4–2.8). However, adults with diabetes in urban areas were less likely to be current smokers than adults in rural areas if they were 45–64 years old (0.5, 0.3–0.9), ≥65 years old (0.2, 0.1–0.3), or female (0.6, 0.5–0.9); had college degree or higher (0.4, 0.3–0.6), PIR 100%–299% (0.6, 0.4–0.9), PIR 300%–499% (0.6, 0.3–0.9), or PIR ≥500% (0.5, 0.3–0.8); or were age ≥60 years at diabetes diagnosis (0.4, 0.2–0.8).

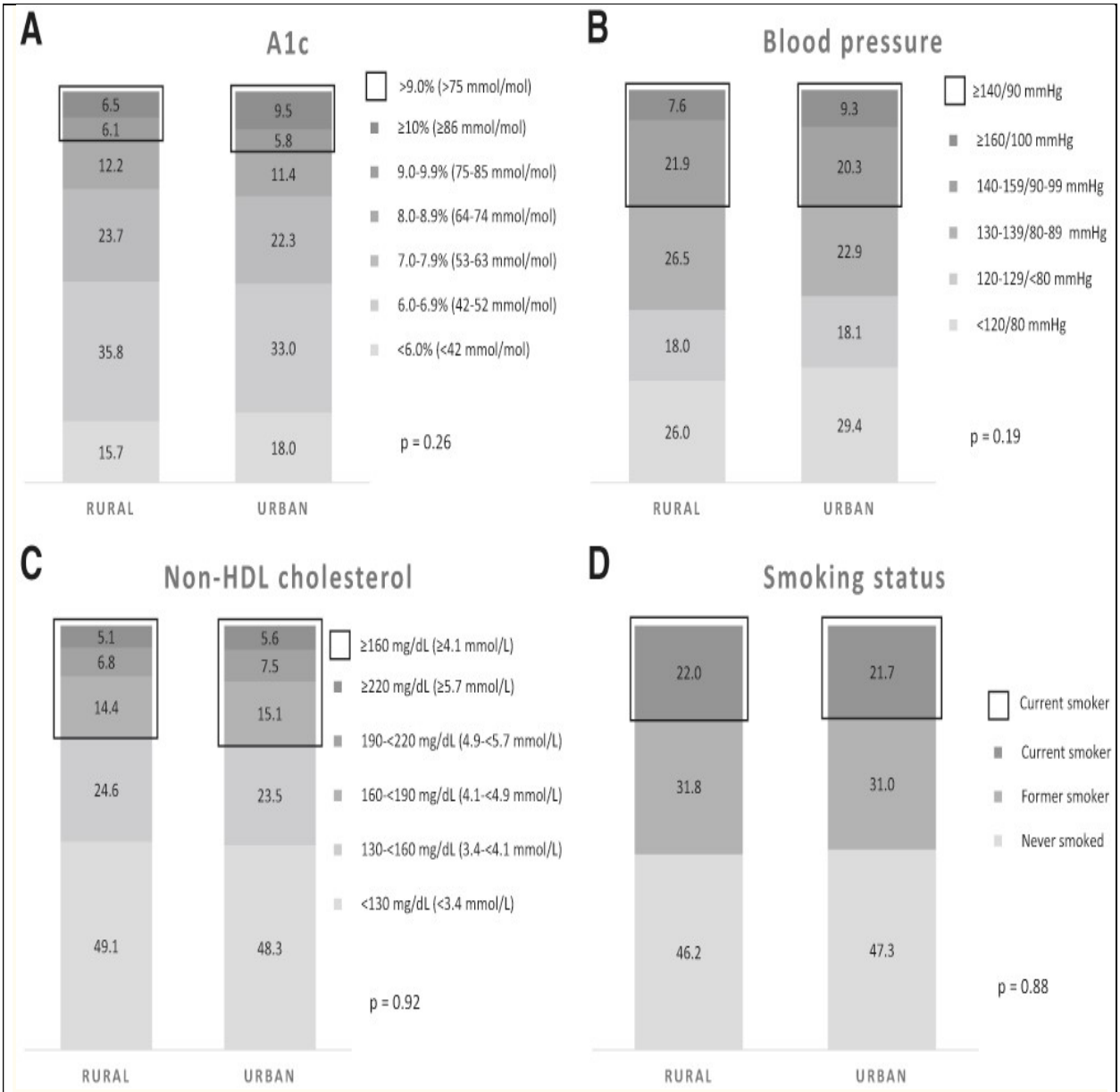

Figure 1—

Distribution of ABCS risk factors for rural and urban residence in U.S. adults with diagnosed diabetes, 1999–2018.

Table 3—

Disparities in ORs of poor ABCS for urban versus rural residence: NHANES, 1999–2018

Urban vs. rural (reference)	A1C >9.0% (>75 mmol/mol)	BP ≥140/90 mmHg	Non-HDL cholesterol ≥160 mg/dL (≥4.1 mmol/L)	Current smoker
Age (years)				
18–44	2.3 (0.9–5.9)	1.3 (0.6–2.8)	1.0 (0.6–1.8)	0.7 (0.4–1.2)
45–64	1.3 (0.5–3.2)	2.1 (0.9–4.4)	0.9 (0.5–1.5)	0.5 (0.3–0.9)
≥65	0.5 (0.2–1.2)	4.4 (2.1–9.2)	0.4 (0.3–0.8)	0.2 (0.1–0.3)
Sex				
Male	1.2 (0.8–1.8)	0.9 (0.7–1.2)	1.0 (0.7–1.5)	1.0 (0.7–1.4)
Female	1.0 (0.7–1.5)	1.1 (0.8–1.4)	1.4 (0.97–2.0)	0.6 (0.5–0.9)
Race/ethnicity				
Non-Hispanic White	1.0 (0.7–1.5)	1.0 (0.7–1.3)	1.1 (0.8–1.5)	1.0 (0.8–1.4)
Non-Hispanic Black	2.2 (1.6–3.2)	1.5 (1.1–1.9)	1.1 (0.8–1.5)	1.3 (0.98–1.7)
Mexican American	2.8 (1.9–4.1)	0.9 (0.7–1.2)	1.5 (1.1–2.1)	0.8 (0.6–1.1)
Other race or multiracial	1.9 (1.3–2.9)	0.9 (0.6–1.2)	1.4 (1.0–2.1)	0.8 (0.6–1.2)
Education (among those aged ≥25 years)				
<High school diploma	2.2 (1.2–4.0)	1.2 (0.9–1.5)	1.3 (0.9–1.8)	0.8 (0.6–1.1)
High school diploma	1.8 (0.9–3.5)	1.0 (0.7–1.3)	1.0 (0.7–1.5)	0.8 (0.6–1.2)
Some college	1.8 (0.9–3.5)	0.8 (0.6–1.1)	1.1 (0.8–1.5)	0.8 (0.5–1.0)
≥College degree	1.1 (0.6–2.2)	0.7 (0.5–1.0)	0.6 (0.4–0.9)	0.4 (0.3–0.6)
PIR				

<100%	1.9 (1.1–3.4)	1.1 (0.8–1.5)	1.2 (0.8–1.9)	1.1 (0.7–1.7)
100–299%	1.1 (0.6–1.9)	1.1 (0.8–1.5)	0.9 (0.6–1.3)	0.6 (0.4–0.9)
300–499%	0.8 (0.4–1.5)	0.8 (0.5–1.2)	0.6 (0.4–1.0)	0.6 (0.3–0.9)
≥500%	1.1 (0.6–1.9)	0.8 (0.6–1.2)	0.7 (0.4–1.1)	0.5 (0.3–0.8)
Health insurance				
Yes	1.0 (0.7–1.5)	1.0 (0.8–1.2)	1.1 (0.9–1.4)	1.0 (0.8–1.4)
No	3.7 (2.6–5.5)	1.0 (0.8–1.3)	2.2 (1.6–3.1)	2.0 (1.4–2.8)
Time since diabetes diagnosis (years)				
0 to <5	1.2 (0.6–2.3)	1.2 (0.8–1.8)	1.1 (0.7–1.6)	1.0 (0.6–1.5)
5 to <15	2.1 (1.1–3.8)	1.5 (1.03–2.2)	0.9 (0.6–1.4)	0.8 (0.5–1.2)
≥15	1.5 (0.8–2.7)	1.9 (1.3–2.9)	0.6 (0.4–0.95)	0.6 (0.4–1.0)
Age at diabetes diagnosis (years)				
<30	1.5 (0.5–4.4)	1.0 (0.5–2.0)	2.0 (0.9–4.5)	1.1 (0.5–2.3)
30 to <45	1.8 (0.6–5.2)	1.4 (0.7–2.8)	2.6 (1.3–5.4)	1.1 (0.5–2.2)
45 to <60	0.8 (0.3–2.3)	1.6 (0.8–3.1)	1.8 (0.8–3.8)	0.8 (0.4–1.6)
≥60	0.4 (0.1–1.1)	2.5 (1.2–5.2)	1.4 (0.7–3.1)	0.4 (0.2–0.8)
BMI (kg/m^2)				
<25.0	0.9 (0.3–2.3)	0.8 (0.4–1.5)	1.8 (0.99–3.3)	0.8 (0.5–1.5)
25.0–29.9	0.9 (0.3–2.4)	0.8 (0.4–1.4)	2.1 (1.1–3.7)	0.6 (0.3–1.1)
≥30.0	0.9 (0.4–2.4)	0.7 (0.4–1.2)	2.3 (1.3–4.1)	0.7 (0.3–1.3)

Data are unadjusted OR (95% CI); each model was unadjusted for covariates.

To our knowledge, this is the first study to investigate trends and disparities in measures of the ABCS in adults with diagnosed diabetes by rural versus urban residence in the U.S. Over 1999–2018, there was no significant difference in ABCS distributions between rural and urban adults with diagnosed diabetes. Yet, over the period, U.S. adults with diagnosed diabetes who resided in urban areas had greater improvements in non-HDL cholesterol and BP than their rural counterparts; there were no significant rural-urban differences in improvement of poor A1C levels or current smoking status. However, there were significant socioeconomic and clinical disparities in the association between poor ABCS management and rural/urban residence. Adults with diagnosed diabetes residing in urban areas were more likely than rural residents to have A1C levels >9.0% (>75 mmol/mol) if they were of race/ethnicity other than non-Hispanic White, had lowest education attainment or PIR or had no health insurance coverage or if there had been 5 to <15 years since diabetes diagnosis. These rural-urban disparities varied in terms of how different sociodemographic and clinical characteristics were associated with poor BP, and poor non-HDL cholesterol, and current smoking.

Although adults residing in rural areas have greater prevalence of chronic conditions and associated risk factors than those in urban areas, we found that overall, among adults with diagnosed diabetes, there were no significant differences between rural and urban areas in the distribution of these ABCS measures. In considering changes across time, there were no statistically significant differences in A1C levels >9.0% (>75 mmol/mol) between rural and urban areas among adults with diagnosed diabetes at each time period during 1999–2018, suggesting similar poor glycemic control in adults with diagnosed diabetes regardless of residence. Additionally, current smoking status in adults with diagnosed diabetes did not significantly change over 1999–2018 and did not differ between those residing in urban areas and those in rural areas. Our overall data from adults with diagnosed diabetes contrasts with data showing greater prevalence of smoking in the general population in rural versus urban areas and greater declines in smoking in urban than in rural areas. However, the sociodemographic and clinical subgroup results in adults with diagnosed diabetes elicited a greater likelihood of smoking in rural versus urban among a few subgroups.

Adults with diagnosed diabetes in urban areas experienced greater improvements in BP and non-HDL cholesterol from 1999–2006 to 2013–2018 than their rural counterparts. During the past decades, BP and lipid medication use has increased among adults with diabetes. Reasons for the difference in improvement of BP and non-HDL cholesterol may be in medication prescribing or adherence among adults with diagnosed diabetes in rural and urban areas that need to be further investigated.

Our data also highlighted critical sociodemographic disparities, emphasizing the multidimensional nature of diabetes management. Of note, minority race/ethnicity and socioeconomically disadvantaged urban adults with diagnosed diabetes were more likely to have poor ABCS measures than rural counterparts.

This is in keeping with recent reports and with the association between geographic structural racial and socioeconomic inequities with health and health outcomes. With the results varying across subgroups in which residential status was more likely to be associated with poor ABCS, epidemiologic research needs to go beyond adjusting regression analysis for the covariates of socioeconomic, demographic, and clinical characteristics, which cannot highlight these disparities. For achievement of health equity in diabetes management, examination of the specificities in the social determinants of health pathways and the impact they have on different populations is needed. Together, our findings suggest that clinical and public health efforts to improve diabetes management will both require tailored strategies that consider the multidimensional contexts of adults with diagnosed diabetes, including socioeconomic barriers to care and to health opportunities.

Since this study was limited in categorization of urban and very rural categories, there were limited numbers of rural adult participants with diagnosed diabetes in each time period. As a result, the rural/urban analyses may have lacked the power to show true associations. Similarly, disparities between sociodemographic and clinical subgroups in poor ABCS between rural and urban residence may not have been detected due to even smaller sample sizes; that said, we combined NHANES cycles to provide stable estimates. Although the impact of multiple comparisons cannot be ignored, this exploratory study had significant findings that seem to be consistent with expectations based on the published literature.

There were a few additional limitations in this study. First, these findings were representative of adults who self-reported being diagnosed with diabetes and not the entire adult population with diabetes. Awareness of diabetes status may vary by rural and urban residence, and adults aware of their diabetes diagnosis may have characteristics and ABCS measures that are different from those of adults unaware of their condition.

Second, this study was of cross-sectional design, and we were able to investigate population-level associations in poor ABCS measures but were unable to examine or quantify individual temporal changes of ABCS measures in a cohort of adults with diagnosed diabetes.

Third, since we encountered differential missingness for rural/urban residence status for each survey cycle (ranging from 3% to 12%), we imputed missing values based on the sampling design true primary sampling unit and strata to minimize any bias that may have been introduced. Nonetheless, it is possible that our limited rural sample size within subgroup analyses may produce compromised U.S. representative estimates. Additionally, we were also limited by the dichotomous definition of rural/urban available from NHANES data and unable to further investigate the different levels of metropolitan areas that can provide a clearer picture of the associations with diabetes care management.

Lastly, NHANES Mobile Examination Center response rates have steadily declined from 80% to the most recent response rate at 49%. While data are not available for response rates by rural/urban residence, it is possible that this decline in response rate may have potentially affected rural residents more so than urban residents. Although weights accounting for nonresponse were used, the ability to calculate estimates representative of the U.S. noninstitutionalized population may become compromised with declining response rates.

Although a few rural-urban differences were observed overall and over time, we noted important differences in poor ABCS in socioeconomically affected groups and other clinical subgroups between adults residing in urban versus rural areas. There is room for improvement when it comes to complete comprehensive care. Clinical and public health professionals need to incorporate evidence-based approaches in addressing sociodemographic barriers to achieve better ABCS measures across the nation but especially in disproportionately affected groups living in urban and rural areas.

Data Sources and Methodology

Epidemiological studies and surveys provide the data needed to understand diabetes trends. Key sources include:

- **International Diabetes Federation (IDF) Diabetes Atlas:** Provides comprehensive data on diabetes prevalence and trends worldwide.
- **World Health Organization (WHO) Global Report on Diabetes:** Offers insights into global and regional diabetes trends and the impact of public health initiatives.
- **National Health and Nutrition Examination Survey (NHANES):** Provides data on diabetes prevalence and risk factors in the United States.
- **European Health Interview Survey (EHIS):** Offers data on diabetes prevalence and health behaviors in European countries.

Chapter 3: Risk Factors and Causes

Understanding the risk factors and causes of diabetes is crucial for developing effective prevention and management strategies. Diabetes is a multifactorial disease influenced by genetic, lifestyle, socioeconomic, and environmental factors.

What leads to diabetes?

Type 1 and type 2 diabetes have different causes, but there are two factors that are important in both. You **inherit** a predisposition to the disease, then something in your **environment** triggers it.

That's right: genes alone are not enough. One proof of this is identical twins. Identical twins have identical genes. Yet when one twin has type 1 diabetes, the other gets the disease, at most, only *half* the time. When one twin has type 2 diabetes, the other's risk is three in four at most.

Type 1 Diabetes

In most cases of type 1 diabetes, people need to inherit risk factors from both parents. We think these factors must be more common in white people because white people have the highest rate of type 1 diabetes.

Because most people who are at risk do not get diabetes, researchers want to find out what the environmental triggers are. One trigger might be related to cold weather. Type 1 diabetes develops more often in winter than summer and is more common in places with cold climates. Another trigger might be viruses. It's possible that a virus that has only mild effects on most people triggers type 1 diabetes in others. Early diet may also play a role. For example, type 1 diabetes is less common in people who were breastfed and in those who first ate solid foods at later ages.

In many people, the development of type 1 diabetes seems to take many years. In experiments that follow relatives of people with type 1 diabetes, researchers have found that most of those who later got diabetes had certain autoantibodies, or proteins that destroy bacteria or viruses (antibodies "gone bad" that attack the body's own tissues), in their blood for years before they are diagnosed.

Your Child's Risk

If you are a man with type 1 diabetes, the odds of your child developing diabetes are **1 in 17**. If you are a woman with type 1 diabetes and your child was born before you were 25, your child's risk is **1 in 25**; if your child was born after you turned 25, your child's risk is **1 in 100**.

Your child's risk is doubled if you developed diabetes before age 11. If both you and your partner have type 1 diabetes, the risk is between **1 in 10 and 1 in 4**.

There is an exception to these numbers: about one in every seven people with type 1 diabetes has a condition called type 2 polyglandular autoimmune syndrome. In addition to having diabetes, these people also have thyroid disease and a poorly working adrenal gland—some also have other immune system disorders. If you have this syndrome, your child's risk of getting the syndrome and developing type 1 diabetes is **one in two**.

Researchers are learning how to predict a person's odds of getting diabetes. For example, most white people with type 1 diabetes have genes called HLA-DR3 or HLA-DR4, which are linked to autoimmune disease. If you and your child are white and share these genes, your child's risk is higher. Suspect genes in other ethnic groups are less well-studied, however, scientists believe the HLA-DR7 gene may put African Americans at risk, and the HLA-DR9 gene may put Japanese people at risk.

An antibodies test can be done for children who have siblings with type 1 diabetes. This test measures antibodies to insulin, to islet cells in the pancreas or to an enzyme called glutamic acid decarboxylase (GAD). High levels can indicate that a child has a higher risk of developing type 1 diabetes.

Type 2 Diabetes

Type 2 diabetes has a stronger link to family history and lineage than type 1, and studies of twins have shown that genetics play a very strong role in the development of type 2 diabetes. Race can also play a role.

Yet it also depends on environmental factors. Lifestyle also influences the development of type 2 diabetes. Obesity tends to run in families, and families often have similar eating and exercise habits.

If there is family history of type 2 diabetes, it may be difficult to figure out whether diabetes is due to lifestyle factors or genetics. Most likely it is due to both. However, studies show that it is possible to delay or prevent type 2 diabetes by exercising and losing weight.

Your Child's Risk

Type 2 diabetes runs in families. In part, this is due to children learning bad habits—eating a poor diet, not exercising—from their parents. But there is also a genetic basis. The good news is, like in adults, it is possible to delay or prevent type 2 diabetes in youth by encouraging healthy food choices, exercise and weight loss.

Genetic Factors

Genetic predisposition plays a significant role in the development of diabetes, particularly type 1 and monogenic forms of diabetes.

- **Family History:** Individuals with a family history of diabetes have a higher risk of developing the condition. The risk is particularly high for type 2 diabetes, where multiple genes contribute to disease susceptibility.

Type 1 and type 2 diabetes have different causes, but there are two factors that are important in both. You **inherit** a predisposition to the disease, then something in your **environment** triggers it.

That's right: genes alone are not enough. One proof of this is identical twins. Identical twins have identical genes. Yet when one twin has type 1 diabetes, the other gets the disease, at most, only *half* the time. When one twin has type 2 diabetes, the other's risk is three in four at most.

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In many people, the development of type 1 diabetes seems to take many years. In experiments that follow relatives of people with type 1 diabetes, researchers have found that most of those who later got diabetes had certain autoantibodies, or proteins that destroy bacteria or viruses (antibodies "gone bad" that attack the body's own tissues), in their blood for years before they are diagnosed.

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Yet it also depends on environmental factors. Lifestyle also influences the development of type 2 diabetes. Obesity tends to run in families, and families often have similar eating and exercise habits.

If you have a family history of type 2 diabetes, it may be difficult to figure out whether your diabetes is due to lifestyle factors or genetics. Most likely it is due to both. However, don't lose heart! Studies show that it is possible to delay or prevent type 2 diabetes by exercising and losing weight.

Genetic Mutations:

Several gene mutations have been linked to the development of type 2 diabetes. These gene mutations can interact with the environment and each other to further increase your risk. Type 2 diabetes is caused by both genetic and environmental factors. Scientists have linked several gene mutations to a higher diabetes risk. Not everyone who carries a mutation will get diabetes. However, many people with diabetes do have one or more of these mutations.

It can be difficult to separate genetic risk from environmental risk. The latter is often influenced by your family members. For example, parents with nutrient-dense and balanced eating habits are likely to pass them on to the next generation

Studies suggest that type 2 diabetes might be linked to genetics. These studies were complicated by the environmental influences that also affect type 2 diabetes risk.

To date, numerous mutations have been shown to affect type 2 diabetes risk. The contribution of each gene is generally small. However, each additional mutation you have seems to increase your risk.

In general, mutations in any gene involved in controlling glucose levels can increase your risk for type 2 diabetes. These include genes that control:

- the production of glucose
- the production and regulation of insulin
- how glucose levels are sensed in the body

Genes associated with type 2 diabetes risk include:

- TCF7L2, which affects insulin secretion and glucose production
- ABCC8, which helps regulate insulin
- CAPN10, which is associated with type 2 diabetes risk in Mexican Americans
- GLUT2, which helps move glucose into the pancreas
- GCGR, a glucagon hormone involved in glucose regulation

People who have a more increased risk of developing Diabetes:

- have prediabetes
- have multiple gene mutations associated with type 2 diabetes
- have a family history of diabetes
- have been diagnosed with high blood pressure
- are age 45 years older
- are overweight
- are physically active less than 3 times a week
- have had gestational diabetes (diabetes while pregnant)
- have given birth to a baby who weighed more than 9 pounds
- have a low level of HDL, known as “good cholesterol”
- have a high level of triglycerides
- were assigned male at birth; people in this group are more likely to have undiagnosed diabetes, possibly because anecdotal evidence indicates they are less likely to regularly visit a doctor
- have depression
- have a history of heart disease or stroke
- have polycystic ovary syndrome (PCOS)

- have acanthosis nigricans

- **Lifestyle Factors**

Lifestyle factors, particularly diet and physical activity, are major contributors to the development of type 2 diabetes.

- **Diet:** Poor dietary habits, such as high consumption of sugary drinks, processed foods, and red meat, increase the risk of type 2 diabetes. Diets high in refined carbohydrates and saturated fats contribute to insulin resistance and obesity.

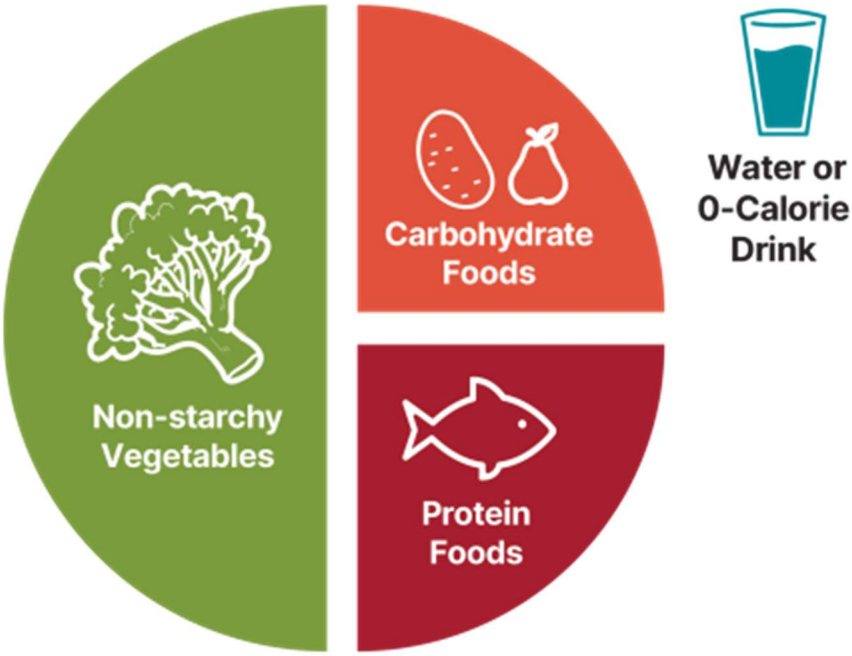
Healthy eating for prediabetes and diabetes not only helps to manage your blood glucose (blood sugar), but it also helps you have a better relationship with food. When you nourish your body with quality foods, it helps your body function at its best.

How to Make Healthy Eating Choices

Informed food choices are essential to living well. Food fuels the body and is a key part of diabetes management. However, no matter what eating plan you follow, there are some basic guidelines that apply across the board.

What all healthy eating plans have in common:

- Non-starchy vegetables as a foundation for the plate
- Lean proteins and plant-based sources of protein
- Quality carbohydrates like starchy vegetables, fruits, whole grains, and low-fat milk
- Less added sugar
- Healthy fats
- Less processed foods
- Water or zero-calorie beverages



Physical Inactivity: Sedentary lifestyles are associated with an increased risk of type 2 diabetes. Regular physical activity helps maintain a healthy weight, improves insulin sensitivity, and reduces the risk of diabetes.

Obesity: Obesity is a significant risk factor for type 2 diabetes. Excess body fat, particularly visceral fat, impairs insulin sensitivity and promotes inflammation.

Obesity and physical inactivity are well-established risk factors for the development of type 2 diabetes. It is estimated that for every 1-kg increase in weight, the prevalence of diabetes increases by 9%. Physical inactivity is associated with increased insulin resistance and poorer glycemic control independent of body weight.

Evidence from randomized controlled trials on three continents has clearly demonstrated that maintenance of modest weight loss through diet and physical activity reduces the incidence of type 2 diabetes in high-risk individuals by ~40–60% over 3–4 years. Lifestyle improvements, including weight control and increased physical activity, are also the cornerstone of diabetes management.

However, despite the known association of obesity and inactivity with diabetes-related morbidity and mortality, there is limited national data reporting the independent association of each risk factor with the prevalence of diabetes and related cardiovascular comorbidities in the U.S. population.

Socioeconomic Factors

Socioeconomic factors influence diabetes risk through access to resources, education, and health behaviors.

In 2010, a 1% increase in per capita income and total tobacco consumption is associated with a 0.92% (95% CI 0.64% to 1.19%) and 0.02% (95% CI 0.006% to 0.047%) increase in diabetes prevalence respectively; and a 1% increase in alcohol consumption is associated with a -0.85% (95% CI -1.17% to -0.53%) decrease in diabetes prevalence. Statistically significant socioeconomic and lifestyle indices positively associated with diabetes prevalence included gross national income; overweight prevalence (BMI>25 kg/m^2); and tobacco consumption. Statistically significant inverse associations with global diabetes prevalence included total population size, unemployment and alcohol consumption.

Statistically significant global lifestyle and socioeconomic determinants of diabetes prevalence include alcohol consumption; tobacco consumption; overweight prevalence; per capita income; total population and unemployment rates. Determinants of diabetes include modifiable risk factors which are consistent at both the micro and macro level and include tobacco consumption and overweight prevalence. Factors which are non-modifiable and warrant further investigation include total population and unemployment rates, which were inversely associated with diabetes prevalence and are a product of other underlying factors. Other determinants such as alcohol consumption were also inversely associated with diabetes prevalence but has been observed to have both negative and positive associations with diabetes at the micro-level. These associations were dependent upon the amount of alcohol consumed.

Global cut-offs point of alcohol consumption is critical to establish global policies to reduce diabetes prevalence. Overall, the use of cross-sectional based study for country level aggregate data is a critical tool that should be considered when making global joint strategies or policies against diabetes in both data analysis and decision making.

Variables	Description
DIAB	Diabetes prevalence (% of population ages 20 to 79). Diabetes prevalence refers to the percentage of people ages 20–79 who have type 1 or type 2 diabetes
ALCHO	Total alcohol consumption per capita (litres of pure alcohol, projected estimates, 15+ years of age). Total alcohol per capita consumption is defined as the total (sum of recorded and unrecorded alcohol) amount of alcohol consumed per person (15 years of age or older) over a calendar year, in litres of pure alcohol, adjusted for tourist consumption.
GNI	GNI per capita is the gross national income, converted to U.S. dollars divided by the midyear population
LIEX	Life expectancy at birth indicates the number of years a newborn infant would live if prevailing patterns of mortality at the time of its birth were to stay the same throughout its life.
OWEI	Prevalence of overweight percentage of adults. Prevalence of overweight adults is the percentage of adults ages 18 and over whose Body Mass Index (BMI) is more than 25 kg/m^2
POP	Total population is based on the de facto definition of population, which counts all residents regardless of legal status or citizenship. The values shown are midyear estimates and expressed in millions
TOBFE	Prevalence of current tobacco use percentage of female adults. The percentage of the population ages 15 years and over who currently use any tobacco product (smoked and/or smokeless tobacco) on a daily or non-daily basis
TOBMA	Prevalence of current tobacco use percentage of male adults. The percentage of the population ages 15 years and over who currently use any tobacco product (smoked and/or smokeless tobacco) on a daily or non-daily basis
TOBT	Prevalence of current tobacco use percentage of adults. The percentage of the population ages 15 years and over who currently use any tobacco product (smoked and/or smokeless tobacco) on a daily or non-daily basis
UNEM	Unemployment is the percentage of the total labour force (modelled ILO estimate). Unemployment refers to the share of the labour force that is without work but available for and seeking employment.

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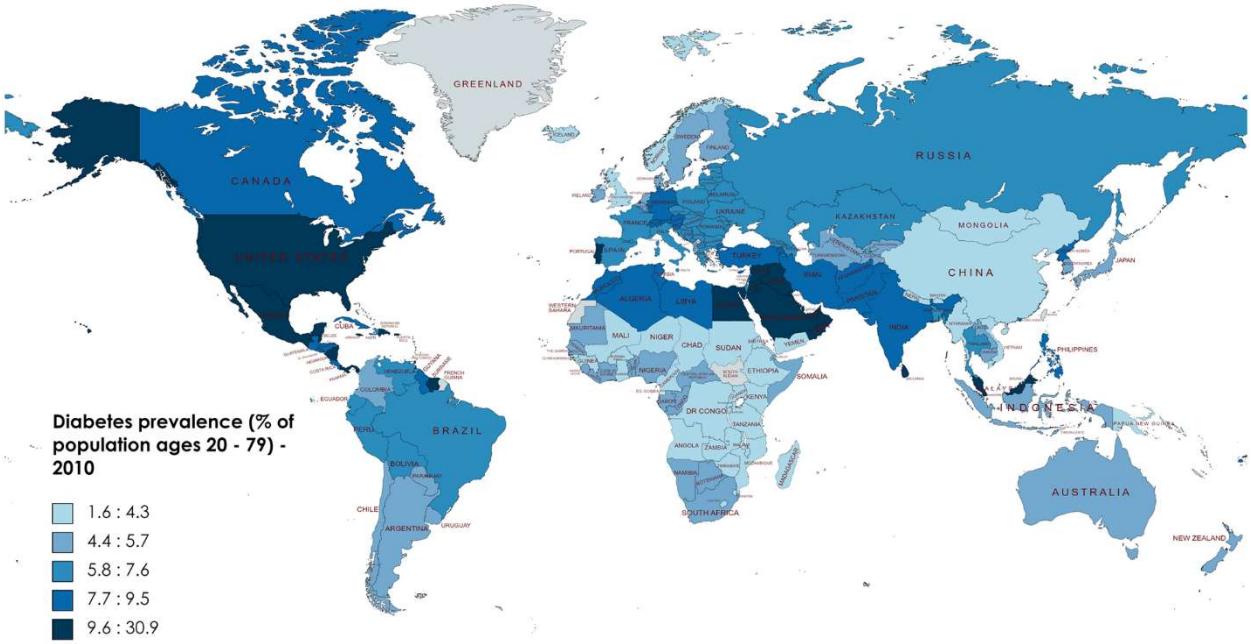

Environmental Factors

Environmental factors, including urbanization and exposure to pollutants, play a role in diabetes development.

- **Urbanization:** Rapid urbanization is associated with lifestyle changes that increase diabetes risk, such as reduced physical activity and unhealthy dietary patterns.

In 2015, the International Diabetes Federation reported that type 2 diabetes (T2D) was the fourth leading cause of death worldwide, with 415 million people affected. Existing literature has examined the contextual effects of urbanization on T2D risk A structural change from agriculture to industrialization has reduced the cost of calories through agricultural innovation and by producing and processing energy-dense food; a recent study has identified changes in obesity prevalence following alternations to agriculture in India.

Meanwhile, the cost of fruit and vegetables has increased due to the limited supply cultivated in less agriculturally productive land. Internal migration contributes to changes in industrial practices and has a role in changing health outcomes. As populations move towards a more urban environment, higher rates of obesity and T2D have been observed, likely because of changes in lifestyles and health behaviors (ie, diet and physical activity) but perhaps also due to the changing socioeconomic make-up of these new urban populations.

Moreover, increasingly, urban sprawl replaces green space with densely populated buildings, reducing outdoor spaces suitable for physical activity. This also hampers proximity and connectivity, where the increase in distance and time to make journeys discouraged society from walking or cycling. Economic literature shows that urban sprawl is more common in higher income countries (HIC) and that it is a proxy for affluence; living in urban environment might also facilitate access to healthcare and preventive programs. Few studies have examined the association between urbanization and T2D at regional/national level finding mostly, but not always, higher prevalence in higher urbanized areas.

It is not clear to what extent urban growth per se is associated with higher prevalence of T2D, or a rapidly increasing urban concentration might promote an obesogenic or diabetogenic environment. Most measures of urbanization in relation to non-communicable diseases were previously found of limited value in measuring the urbanization process. The aim is to investigate the association between urbanization and T2D at country level, worldwide, and to examine the role of the main potentially modifiable lifestyle risk factors (physical inactivity, sugar consumption and obesity) in mediating this association. The potential effect modification of gross domestic product (GDP) was also explored.

Urbanization

There is no consensus on how to measure urbanization at country level; few indicators have been suggested, providing different proxy measures. Data on urbanization measured by urban percentage (UP), that is, the proportion of a population living in urban areas as defined by national statistical offices, was collected for 207 countries from the 2015 World Bank Development Indicators. UP, despite being the most used and widely available measure because of its simplicity, relies on country-specific definition of what it is urban, potentially leading to different ranks of urbanization when several countries are considered. Therefore, also data on the agglomeration index (AI) in 2008 was obtained for 162 countries from The World Bank World Development Report. AI is a composite measure of population density, size and travel time to the nearest urban city. Population density is based on the average of two global gridded population data sources—Global Rural-Urban Mapping Project and LandScan.

The population size in a defined 'large' urban center used for this analysis was 100 000 inhabitants. Travel time to the nearest urban city is calculated by a cost–distance model that estimates travel time to the city over the average travel speeds, based on GIS data, between the transport network and off-road surfaces. These components are aggregated, with the proportion of this number to that country's total population being the AI. This measure is designed to quantify the degree of settlement concentration in order to capture the difference between large cities growing bigger from many small cities emerging. Also, AI includes only locations that satisfy all three components, transcending country-specific and ad hoc definition discrete entities, such as cities and administrative boundaries. However, AI is sensitive to the chosen threshold values used to define the components.

- **Pollution:** Exposure to environmental pollutants, such as air pollution and endocrine-disrupting chemicals, has been linked to an increased risk of diabetes. These pollutants may interfere with metabolic processes and insulin function.

Along with rapid socioeconomic development worldwide, the harmful health effects of air pollutants have received increasing attention. On the basis of their existing state in the atmosphere, pollutants can be divided into gaseous pollutants and atmospheric particulates. Gaseous pollutants include sulfur compounds, nitrogen compounds, carbon oxides, hydrocarbons, and halogen compounds; atmospheric particulates comprise total suspended particulates, inhalable particles (PM10), fine particulate matter (PM2.5), and ultrafine particulate matter. Reports from the Global Burden of Disease, Injuries, and Risk Factors Study 2017 indicated that air pollution was the eighth leading risk factor for death. A total of 2.94 million deaths have been attributed to ambient particulate matter pollution globally. Furthermore, a large number of studies have found that air pollution has been linked to respiratory disease, cardiovascular and cerebrovascular diseases, and metabolic syndrome.

Diabetes is a metabolic disorder caused by genetic and environmental factors that results in insufficient insulin secretion and impaired biological effects and is considered one of the major contributors to the global burden of disease and premature death. In recent years, the prevalence of diabetes has progressed incessantly in both developed and developing nations. Furthermore, current studies indicate that air pollutants may be associated with impaired glucose metabolism, insulin resistance (IR), and type 2 diabetes mellitus (T2DM).

Effects of air pollution exposure on T2DM in subpopulations

Subpopulations were also studied to investigate the association between air pollution and T2DM among women in general, pregnant women, obese individuals, and elderly people. Honda and colleagues evaluated the association between long-term average air pollutant levels and the prevalence of T2DM and HbA1c levels among older Americans and found that air pollution was associated with abnormal glucose metabolism and T2DM in elderly participants. This association was stronger among elderly individuals and was supported by previous studies. Shen and colleagues conducted a case-control study on 6717 mothers with gestational diabetes mellitus (GDM) in Taiwan and concluded that higher maternal pre- and post-pregnancy exposures to PM2.5 and SO2 were associated with a modestly elevated, but significant, risk of GDM. A large cross-sectional study in Sweden including 81,110 pregnant women showed that the prevalence of GDM during the second trimester increased with NOx exposure (OR = 1.69, 95% CI: 1.41–2.03).

However, a cohort study of more than 7000 pregnant women in the Netherlands found no association between air pollution exposure and GDM. Another study in the United States of 2093 women showed that exposure to air pollutants during pregnancy was associated with impaired glucose tolerance (IGT) (OR = 2.63, 95% CI: 1.15–6.01) but not GDM (OR = 0.71, 95% CI: 0.35–1.42). In addition, evidence in the Danish Nurse Cohort Study showed that PM may be the most relevant pollutant for diabetes development among women, and that nonsmokers, obese women, and heart disease patients may be more susceptible. Although several previous studies did not find significant evidence of an association between T2DM and air pollutants among women, a meta-analysis that included the above studies showed that the association was stronger in women than in men. Interestingly, Lim and colleagues found that the diabetes mortality risk attributable to air pollution was significantly decreased among those who consumed higher levels of fruits and had a lower BMI, suggesting that higher fruit consumption and weight loss are recommended, especially for susceptible populations.

The sex-, age- and BMI- specific differences seen in some of these studies may relate to true differences in biologic susceptibility. The current studies noted that elderly, female, and obese participants were more susceptible to T2DM under exposure to air pollution. On the other hand, it is also possible that subpopulations may be subject to exposure assessment error, particularly men, younger people, and individuals with lower BMIs who tend to be more mobile than other subpopulations. Research on GDM and air pollution is scarce, with inconsistent estimates, and this specific subpopulation is of concern and merits further investigation.

Effects of air pollution exposure on T2DM in countries with different economic development levels

Air pollutants vary between developed and developing countries. A population-based cohort study conducted in Canada to investigate the link between exposure to ultrafine particles and NO2 and T2DM showed that air pollution may increase the risk of T2DM. Hernandez and colleagues used data from the US Centers for Disease Control to conduct a Poisson regression analysis examining associations between each air pollutant (per 10-unit increase) and T2DM, and found that the diabetes prevalence ratios of PM2.5 and ozone were 1.10 and 1.06, respectively. Another cross-sectional study in a Swiss population also found a similar significant relationship between PM10 and T2DM. A large cohort study evaluated the link between long-term exposure to air pollution and the occurrence of T2DM in Rome and found that long-term exposure to nitrogen oxides was associated with prevalent diabetes, while NOx and O3 exposures were associated with incident T2DM. However, the few cohort studies conducted in developed countries indicated no significant association between PM and T2DM. Kramer and colleagues conducted a cohort study among 1775 nondiabetic women in Germany to examine the association between traffic-related air pollution and incident T2DM and showed that PM10 was not significantly associated with T2DM (HR = 1.16, 95% CI: 0.81–1.65). Similar null results were also presented by three additional studies.

These inconsistent conclusions might be explained by the subgroup populations being targeted and the different methodologies used. Yang and colleagues examined the association between exposure to PM2.5 and T2DM among 11,504 Chinese adults in a large cross-sectional study, finding that PM2.5 was significantly associated with T2DM (adjusted OR was 1.27 for each 10 $\mu g/m^3$ increase in ambient PM2.5) A large cross-sectional study conducted in China with 15,477 adult participants using a random number generator and multistage cluster sampling method also demonstrated that long-term exposure to air pollution was associated with an increased risk of T2DM in a Chinese population. Studies focusing on this link in developing countries are mainly documented in mainland China, which may contribute to a high risk of bias. Further studies in developing countries are needed to expand the conclusions, given that both T2DM prevalence and air pollution concentrations are reported to be much higher in those countries. The burden of T2DM attributed to PM2.5 exposure varied substantially between geographical locations and was more serious in low-income and lower-to-middle income countries However, high-quality studies in underdeveloped countries are scarce and these areas require further research.

- **Built Environment:** The built environment, including the availability of parks, recreational facilities, and healthy food options, influences physical activity levels and dietary habits.

Evidence has mounted that built environment characteristics are associated with diabetes risk. Further, there is additional evidence regarding mechanisms that may underlie this association. Major modifiable risk factors for T2DM include body mass index (BMI), physical activity, and diet. For this reason, much of the work examining mechanisms that link the built environment to diabetes risk has focused on associations between the built environment and these factors. Below, we discuss evidence for an association between built environment factors and diabetes risk itself, along with evidence regarding an association between the built environment and diabetes risk factors. In interpreting this evidence, we point out a major issue in studying the built environment: challenges in distinguishing the role that compositional characteristics (i.e., those individual-level characteristics of the people living in an area, for example, education, income, and race/ethnicity) and contextual characteristics (i.e., the characteristics of the environment itself such as housing inventory, parks, etc.) play in diabetes risk, and how these factors may interact. Distinguishing these features requires data on both levels (individual and area) and sometimes sophisticated statistical analysis. Some studies are able to do this well, but many studies are less able to do so, often because they lack data on individual socioeconomic circumstances. Therefore, it can be difficult to determine whether it is specific features of the built environment that drive the association, or individual-level factors. related field to advance, and for policies that affect features of the built environment to lower diabetes risk, we will need more sophisticated understanding of the way in which built environment features causally relate to diabetes.

- **The Built Environment and Diabetes Prevalence and Incidence**

- We studied the relationship between the built environment and diabetes risk. In general, we focus on two key aspects of the built environment—features that encourage physical activity, such as walkability and green spaces, and the food environment.

Several cross-sectional studies support an inverse relationship between walkability and T2DM risk. Walkability was associated with a lower risk of T2DM in a systematic review of 60 articles from high-income countries including the United States, Canada, Germany, and Australia by Dendup et al. Among older adults, those who lived in the greenest neighborhood quartile had a lower risk of developing diabetes (HR 0.81, 95% CI 0.67 – 0.99, P= 0.04) with relatively little change in risk after adjusting for age, sex, BMI, family history of diabetes or socioeconomic status, in a United Kingdom study.

The risk of T2DM was lower in neighborhoods with more green space, with the strongest association among participants who lived in neighborhoods with 40 to 60% green space (OR 0.87 95% CI 0.83, 0.92) in an Australian cohort study conducted among adult middle-aged and older adults.

While there is an inverse association between increased walkability and open spaces and diabetes incidence and prevalence, this association is modified by socioeconomic status and immigration status. The impact of socioeconomic status on the relationship between the built environment and T2DM was further demonstrated in a cross-sectional study of 512,061 Swedish adults conducted by Sundquist et al. Greater neighborhood walkability was associated with greater T2DM incidence (OR 1.33, 95% CI 1.13 – 1.55) when not adjusting for individual socioeconomic factors. However, this association was no longer significant once these factors were adjusted for. This finding highlights the importance of considering both compositional and contextual factors in understanding the relationship between the built environment and diabetes.

Specifically, associations that may appear to be driven by contextual (aspects of the environment itself like walkability) factors can turn out to be related to compositional (aspects of those who live in the environment, like low socioeconomic status) factors when consideration is given to both possibilities. Similarly, the relationship between immigration status, built environment, and diabetes was further explored in a retrospective cohort study among recent immigrants (214,882 individuals) and long-term residents (1,024,380 individuals) of Toronto, Canada. Area walkability was inversely related to incidence of diabetes among long-term residents in Toronto in both men (RR 1.32, 95% 1.26 – 1.38) and women (RR 1.24, 95% CI 1.18 – 1.31). The magnitude of this association was greater among recent immigrants (RR 1.58, 95% CI 1.42 – 1.75 for men; RR 1.67, 95% CI 1.48 – 1.88 for women).

The longitudinal relationship between changes in the built environment and incident diabetes and diabetes-related outcomes has also been established. In a systematic review and meta-analysis of 36 studies in the United States, Canada, Sweden, and Australia, increased neighborhood walkability was associated with decreased incident hypertension, obesity, T2DM, and cardiovascular disease events. Most studies assessed in this review had a duration of 5 years or longer with data collection at 3 or more time points.

A time series analysis from 2001 to 2012 of 8777 neighborhoods and 32767 individuals in Southern Ontario found that the prevalence of overweight/obesity increased in the neighborhoods that were least walkable at baseline (absolute change, 5.4% [95% CI, 2.1%−8.8%]) but did not increase in the most walkable neighborhoods (absolute change, 2.1% [95% CI, −1.4% to 5.5%]). In a meta-analysis of 6 studies, increased walkability was associated with lower T2DM risk (RR 0.79, 95% CI 0.72 – 0.87). More green space was non-significantly associated with lower T2DM risk (RR 0.90, 95% 0.79 – 1.03), though the magnitude of this association is small.

Evidence for the association between the food retail environment and diabetes risks suggests that the availability of healthy food outlets decreases T2DM risk. In a systematic review of 109 articles, the presence of fast-food and convenience stores was associated with higher T2DM prevalence and risk. In two studies in the United Kingdom, close proximity to fast food outlets was associated with greater T2DM risk.

The odds of having T2DM (OR = 1.02, 95% CI 1.00 – 1.04) and obesity (OR = 1.02, 95% CI 1.00 – 1.03) were greater in neighborhoods with more fast food outlets in a cohort study of 10461 participants[7], and the odds of T2DM were greater in those with the highest exposure to restaurants and cafeterias, compared with those who had no exposure (OR 1.13, 95% CI 1.05 – 1.21), in a cross-sectional study of 502,635 adults. Individuals who lived farther away from fast-food outlets had lower odds of T2DM (OR 0.84, 95% CI 0.78 – 0.91) compared with those who lived closest. Also, in a prospective cohort study of more than 4.5 million individuals in Sweden, health-harming food outlets (fast-food outlets, bars, or pubs) were associated with higher odds of prevalent (OR = 1.85, 95% CI 1.51 – 2.26) and incident (OR = 2.11, 95% CI 1.57 – 2.82) T2DM. Further, individuals who changed locations during the study had a higher odds of incident T2DM (OR 3.67, 95% CI 2.14 – 6.30) when they moved to an area with more (vs. fewer) health-harming food outlets.

- **The Built Environment and Diabetes Risk Factors**

Aside from examining diabetes risk directly, a number of studies have found that features of the built environment are associated with risk factors for developing diabetes. Major risk factors examined have been physical activity, overweight/obesity, and insulin resistance.

Increased physical activity has been associated with increased walkability. In a systematic review of 44 studies conducted in Australia, Canada and Belgium, Durand et al. explored the relationship between the physical environment and degree of physical activity and found that open space preservation was associated with increased physical activity and higher rates of walking was associated with range of housing choices, mixed land use, development towards existing communities, and compact building design. Walkability and street connectivity have been related to transportation-related physical activity, and leisure activity has been most frequently associated with road and sidewalk conditions, as well as safety. Across 103 articles concerning children and adolescents, the most consistent correlations in children were between level of physical activity and walkability, traffic speed, volume, land use mix, residential density, and access or proximity to recreational facilities. Among adolescents, land-use mix and residential density were the strongest correlates for physical activity.

Street connectivity and availability of recreational equipment has a positive association with physical activity. Higher street connectivity was significantly related to lower sedentary time (b = 1.93, 95% CI 1.11 – 4.96), in a cross-sectional study of 5712 participants in 17 urban areas across 12 countries. The availability of recreational equipment was associated with various types of physical activity in a systematic review of 47 observational studies. Residential density (b = 1.01, 95% CI 1.00 – 1.01), intersection density (b = 1.07, 95% CI 1.01 – 1.13), public transport density (b = 1.04, 95% CI 1.02 – 1.06), and number of parks b = 1.15, 95% CI 1.03 – 1.27) were positively associated with physical activity in a cross-sectional study of 6822 adults in 14 cities from 10 countries though these effects were all modest. This suggests that zoning and urban planning may play a role in increasing physical activity in urban areas. Finally, federal housing assistance has been associated with greater physical activity.

Changes to the built environment that increase walkability of neighborhoods, improve recreational spaces, and enhance transportation infrastructure could increase physical activity in both children and adults. Examples of these changes are construction of new sidewalks and crosswalks, installation of raised platforms and ‘zebra’ crossings to improve pedestrian safety, development of new greenways, installation of fitness and playground equipment, and park renovations.

This evidence suggests that interventions to enhance the physical infrastructure of neighborhoods may promote both transport (i.e., getting to and from locations such as work or school) and recreational physical activity.

Several studies have also examined the relationship between the built environment and overweight/obesity. One way of understanding the relationship between the built environment and overweight/obesity is via neighborhood deprivation. Neighborhood deprivation is a measure that accounts for income, poverty, housing, education, employment and occupation. [33] A greater degree of neighborhood deprivation was modestly associated with higher BMI (greater than 35) (RR 1.22, 95% CI 1.12 – 1.31) and hemoglobin A1c of 9% or greater (RRR 1.33, 95% CI 1.16 – 1.52) even after adjusting for individual factors in a cross-sectional study of 20,188 adults with chronic diseases in 19 Northern California counties.

Another way to conceptualize the relationship between the built environment and overweight/obesity is to consider features of the environments at different scales: the macro-, meso-, and micro-levels. At the macro-level, the built environment is classified by degrees of urban sprawl and compactness using density, mix, centered ness, and street connectivity. Areas with greater sprawl were associated with higher rates of obesity than more compact ones. Additionally, residents living in more compact areas had lower BMI values and rates of chronic cardiometabolic conditions like hypertension, coronary artery disease, and diabetes. The meso-level described areas within a 1 km distance of individuals, characterizing them by land use mix, residential density, and street connectivity.

The investigators found that of these 3 measures, land use mix was the most strongly associated with obesity and that each quartile increase in land use mix was associated with a 12.2% reduction in likelihood of obesity accounting for gender and ethnicity. They also found that walkability of neighborhoods and proximity to parks and recreational spaces were of significance. Finally, proximity to supermarkets and grocery stores was associated with lower rates of obesity, while proximity to, or presence of, convenience stores and fast food were associated with higher rates of obesity. Highlighting the importance that area planning can play, for each additional kilometer walked, there was a 4.8% decrease in odds of obesity and for each hour spent in a car per day there was a 6% increase in odds of obesity, in a cross-sectional study including 10,878 participants in the metro Atlanta area. Therefore, planning decisions that influence how much one walks vs. spends time in a car may have a powerful effect on area obesity prevalence. By contrast, commercial density (measured as number of commercial facilities per hectare where commercial facilities are non-residential buildings used to conduct business) was associated with a 0.75 kg/m^2 increase in BMI for each additional commercial facility per hectare in a cross-sectional study conducted in rural Vermont.

This was surprising, as most prior studies found that lower BMIs were associated with compactness and increased density. This suggests that the relationship between density and obesity may vary in urban versus rural contexts.

There have been a few longitudinal studies examining changes in the food environment and its effects on diabetes outcomes. Improvements in the food environment, such as increases in supermarkets, grocery stores, and produce venues supplying healthful foods in a person's neighborhood, was associated with weight loss among adults with diabetes who maintained the same residence over 5 years, in a longitudinal cohort study of 194,652 individuals in Northern California conducted by Laraia et al. However, magnitude of the association (1 pound lost for each standard deviation improvement in food environment) was small and unlikely to be clinically meaningful.

Case Studies

Examining case studies provides insights into how different risk factors contribute to diabetes development.

- **Case Study 1:**

L.S. is a 52-year-old Caucasian woman who was diagnosed with type 2 diabetes in 1988. She developed hypertriglyceridemia 3 years later and hypertension 9 years later. Other medical problems include obesity and diverticulosis. She arrives for screening to determine eligibility for a clinical research protocol using once-daily insulin. The physical exam reveals a height of 64 inches, a weight of 181 lb, a body mass index of 31 kg/m^2, and a waist circumference of 40 inches.

Blood pressure, well controlled on 20 mg lisinopril (Prinivil) daily, is 104/70 mmHg. Laboratory results reveal a fasting lipid panel as follows: total cholesterol 214 mg/dl, triglycerides 940 mg/dl, direct HDL cholesterol 24 mg/dl, an invalid LDL cholesterol unobtainable because of the hypertriglyceridemia, and a free fatty acid of 1.1 mEq/l (normal range 0.1–0.6 mEq/l). Hemoglobin A_{1c} (A1C) is 9.5%, and fasting blood glucose (FBG) is 304 mg/dl.
When called to discuss the finding of severe hypertriglyceridema, the patient commented that she had previously fasted triglycerides as high as 3,000 mg/dl.
L.S. is currently taking metformin (Glucophage), 1,000 mg twice daily, and glipizide (Glucatrol XL), 10 mg twice daily, to control her blood glucose. She is also on gemfibrizol (Lopid), 600 mg twice daily, for hypertriglyceridemia and estradiol (Estraderm) for menopause (topical estrogen does not induce hypertriglyceridemia).

Questions

1. What nutritional modification would be effective in rapidly lowering serum triglycerides when the patient is at risk of pancreatitis?
2. What treatment strategies can be employed to lower triglycerides, and how effective are they?
3. How can nutritional modifications improve insulin resistance?

Discussion

Type 2 diabetes carries a two- to fourfold excess risk of coronary heart disease. The most common pattern of dyslipidemia in patients with type 2 diabetes is elevated triglycerides and decreased HDL levels. Although coexistent increases in small, dense LDL cholesterol particles—not the triglycerides themselves—may be responsible for the increase in cardiovascular risk, hypertriglyceridemia poses a significant burden on society.

In type 2 diabetes, characterized by insulin resistance and insulin deficiency, the pathophysiology of hypertriglyceridemia is an increased hepatic production of triglycerides as well as a decreased lipoprotein lipase activity leading to slower breakdown of VLDL cholesterol and chylomicrons. The American Diabetes Association (ADA) Clinical Practice Recommendations list serum triglycerides ≥400 mg/dl and an HDL level <45 mg/dl for women as indicative of high risk of coronary heart disease.

By both ADA and National Cholesterol Education Program (NCEP III) guidelines, the first goal for this patient is to lower triglycerides to prevent pancreatitis, which not only can result in hospitalization, but also is potentially lethal. Although L.S. is already on the maximum dose of gemfibrozil, her triglycerides are still inadequately controlled.

With triglycerides in this range, she should be alerted immediately to the fact that any alcohol, even that found in over-the-counter cold remedies can trigger pancreatitis until her serum triglycerides are brought down to a safer range (<500 mg/dl). In addition, a single high-fat meal can also trigger pancreatitis.

A severely restricted fat intake (<10% of daily kcal) can effectively bring down serum triglycerides by 20% per day until triglycerides are <500 mg/dl. A diet in which fat is so severely restricted usually brings about weight loss as well. A loss of 2.5 kg body weight would bring an expected 15–20% decrease in serum triglycerides. In addition, aerobic exercise can help to lower serum triglycerides by 10–15%.
Interventions to further decrease serum triglycerides to <200 mg/dl, increase HDL to 45 mg/dl, and decrease LDL to <100 mg/dl should be attempted to decrease the risk of coronary heart disease.
At the first clinic visit, L.S. was advised of the risk of pancreatitis and advised to forego any alcohol and to adhere to severe fat restriction until she has a fasting serum triglyceride level <400 mg/dl. She and her husband are both from the South, and their traditional Southern fare used quite a bit of salt pork, which deleteriously augmented the saturated as well as total fat in her diet. She had been advised to "watch her weight" when her triglycerides were in the 3,000 mg/dl range, but she had been unable to follow that recommendation.

Between clinic visits, L.S. was given written information about a low-fat (10% of kcal) diet, including lists of foods to restrict and foods to encourage until a more thorough meal plan could be developed based on an assessment of her previous dietary patterns. She was advised that this was a short-term, severe dietary change. She had already instituted an exercise program, walking for 1 hour, five times a week regularly.

Two weeks later, when L.S. returned to clinic after following the suggested fat restriction, her lab results showed the following lipid profile: serum total cholesterol 193 mg/dl, serum triglycerides 355 mg/dl, direct HDL cholesterol 32 mg/dl, and LDL cholesterol 90 mg/dl. Her A1C had dropped to 8.8% with no change in therapy for her diabetes, and her FBG was 158 mg/dl. Her fasting free fatty acid level was 0.7 mEq/l. Her weight had dropped by 3 lb.
During this visit, medical nutrition therapy (MNT) was initiated, and the patient was put on 10 units of 75/25 insulin before dinner.

Six weeks later, her A1C had dropped further, to 7%, her FBG was 110 mg/dl, and her weight was down another 2 lb. Her lipid profile was as follows: total cholesterol 181 mg/dl, triglycerides 299 mg/dl, direct HDL cholesterol 32 mg/dl, and LDL cholesterol 89 mg/dl.
Her fasting free fatty acid level was now 0.6 mEq/l, the upper level of normal. Meal plan records showed that she was consuming ~1,500 kcal/day and getting ~25% of daily kcal from fat.

Commonly, controlling hyperglycemia leads to a decrease in triglycerides. However, in this patient, the clearing of serum triglycerides, the restricted saturated fat, and the weight loss had a substantial impact on improving glucose tolerance without adding further diabetes oral agents. Studies have shown that dietary fat, primarily saturated fat, has adverse effects on insulin sensitivity. Restricting fat intake, especially saturated fat, resulted in a better metabolic profile in regard to both glucose tolerance and fasting serum triglycerides.

Lifestyle changes had been recommended previously; why was L.S. successful this time when she hadn't been before?
The patient offered the following comments when asked this question
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- "I was handed written information, but concern about the numbers (hypertriglyceridemia) was never conveyed."
- "They tell you what you need to do, but not how or why to do it."
- "No one sat down and talked with me. I never received individualized attention."
- "If my triglycerides were potentially harmful, why did they not see me sooner than 3 months? Three months was the usual time between visits and again they conveyed no concern."

In previous attempts to encourage this patient make lifestyle changes, the compliance approach was used, but the benefits of self-care, the costs of not complying, the susceptibility to pancreatitis and cardiovascular disease, and the severity of such elevated triglycerides were not conveyed. A referral to an educator, time spent assessing eating patterns and teaching alternatives, and more frequent visits or follow-up serve to convey the importance of recommended lifestyle changes. MNT coupled with an empowerment approach through which patients are the primary decision makers is important.
Although lifestyle changes are always recommended as first-line therapy, the approach to helping patients achieve these lifestyle changes in busy office practices is too often insufficient. A new Medicare benefit effective January 2002 allows patients with diabetes access to insurance coverage for MNT. Evidence-based research shows that MNT provided by a registered dietitian experienced in the management of diabetes is clinically effective.

Clinical Pearls

- Reducing dietary fat improves body weight, which in turn improves glucose tolerance and hypertriglyceridemia.

- There is evidence that saturated fat may elevate plasma glucose by way of increasing insulin resistance.

- MNT for hypertriglyceridemia may be divided into three parts:

1. When fasting triglycerides are ≥1,000 mg/dl, restrict dietary fat to 10% of kcal until fasting triglycerides fall to <500 mg/dl.

2. For fasting triglycerides between 1,000 and 500 mg/dl, *a*) reduce saturated fat to <7% of energy and dietary cholesterol to 200 mg/day; *b*) increase viscous (soluble) fiber to 10–25 mg/day; *c*) encourage modest weight loss (5–7% of body weight); and *d*) increase physical activity. Monounsaturated fats or carbohydrates can be used to substitute for the decrease in saturated fats.

3. For fasting triglycerides <500 mg/dl, encourage weight loss and a decrease in simple sugars in addition to the above reduction in saturated fat.

- **Case Study 2**

Max (a pseudonym) is a 17-year-old girl who was diagnosed with type 1 diabetes 4 years ago at the age of 13 years. She and her mother were shocked and upset by the diagnosis, and both felt its management would be too great a task to take on by themselves.

Max is an only child and lives with her mother, a single parent. She attends the local state comprehensive school and is popular with her peer group. Her mother was very involved in her care and diabetes management from the onset. Despite this, her diabetes control deteriorated over time In October 2012, her HbA_{1c} was 56 mmol/mol (7.3%); however, over the next year, this increased to 84 mmol/mol (9.8%) in July 2013. She found it difficult to count the carbohydrate portions in her food and her injections were hurting much more than when she was first diagnosed. She also expressed a fear of hypoglycemia and of "looking stupid" in front of her friends.

Max and her MDT discussed treatment options to improve her glycemic control. She refused insulin pump therapy but agreed to a blood glucose monitor and bolus advisor to assist with her regimen of multiple daily insulin injections (MDI). She is now using the bolus advisor confidently and has had regular one-to-one sessions with a psychologist. She is having fewer hypoglycemic episodes and her HbA_{1c} has improved; in January 2016 it was 69 mmol/mol (8.5%) and in April 2016 it was 58 mmol/mol (7.5%).

Diagnosis

Max and her mother were extremely shocked and upset by the diagnosis of type 1 diabetes and the potential severity of the condition and intense management required. Both felt it would be too great a task to take on by themselves.

Kübler-Ross and Kessler suggested that a diagnosis of diabetes is a life-changing event comparable to the experience of loss, and that children and families will often go through the five stages of grief defined by Kübler-Ross. They use this as a coping strategy to enable them to eventually acknowledge the condition. However, many families never reach the fifth stage of acceptance, and many will fluctuate between the stages.

Although Max and her mom did accept the diagnosis eventually, at times both reverted to the earlier stages of grief. The diabetes MDT supported the family from diagnosis and will continue to support them throughout their time within the pediatric diabetes service, through the transition period with both pediatric and young people's teams, until discharged to adult diabetes care.

The diabetes MDT was established after the Best Practice Tariff was introduced in 2012. It consists of doctors, nurses, dietitians, a psychologist and a personal assistant. It is well recognized that the MDT needs to work together in close cooperation to achieve good practice, and this can be strengthened by using written protocols, guidelines and targets. Logic would suggest that centers with MDTs and the same approaches and treatment regimens would have similar outcomes, yet the Childhood Diabetes Study Group has shown this is not the case. In terms of glycemic control, there were notable differences in patient outcomes across 21 diabetes clinics, all of which were committed to MDT-based practice. Although factors such as age, type of insulin regimen and socioeconomic status were shown to have some influence over specific outcomes, they did not explain the apparent differences between these clinics.

Family/social history

Max is an only child and lives with her mother, a single parent. Dates suggest rapid social change, the past 20 years has seen a marked increase in the number of mother-headed single-parent families. Max attends the local state comprehensive school, where she is generally doing well. She is popular with her peer group. Studies also suggested that peer relationships are important in diabetes management, as children and young people may receive considerable emotional support from their friends. However, on occasions, Max's peer relationships have had a counterproductive effect on her, and she feels she is different from her friends as the only one who has diabetes.

This at times affects her self-esteem and impacts her diabetes control. Max's mother was very involved in her care and diabetes management from the onset. It is also a known fact that parents typically take on most of the responsibility for management of diabetes when children are young or newly diagnosed.

Deterioration in diabetes control

Max's diabetes control had deteriorated since her diagnosis, her HbA_{1c} was 56 mmol/mol (7.3%), which indicated a good level of diabetes control and a reduced risk of diabetes complications, At her subsequent diabetes clinic appointments up to July, she reported that "nothing had really changed," except she "didn't have time to think about her diabetes," although she felt guilty because she knew she could make herself ill and her mum would get upset. She stated that it was hard counting the carbohydrate portions in her food and her injections were hurting much more than when she was first diagnosed. Her height and weight remained static.

Diabetes care is greatly influenced by psychosocial factors when they obstruct people's ability to manage their diabetes and achieve good metabolic control. A team-based approach to addressing an individual's ability to cope is critical It is important for healthcare professionals to be aware of how CYP think at the different stages of their development, as their understanding of illness and chronic health conditions is often greater than that of their peers. Jean Piaget (1896–1980) investigated cognitive processes in children, calling them "schemas". By the time children reach around 12 years of age, they can describe illness in terms of non-functioning or malfunctioning of an internal organ or process. Later in development they can appreciate that a person's thoughts or feelings can affect the way the body functions, which demonstrates an awareness of psychological factors

Spear proposed that we can begin to understand how young people with type 1 diabetes think, feel and behave if we consider the cognitive and biological changes that occur during adolescence. Glasper and Richards suggested there is now a growing awareness that CYP are able to make their own decisions if given information in an age-appropriate manner. Gillick competence identifies children aged under 16 years as having the capacity to consent to their own treatment if they understand the consequences.

Butler et al suggest that adolescence is a time of upheaval when young people have to deal with the influence of peers, school life and developing their own identity, as well as all the physiological changes that occur. Young people with type 1 diabetes have the added responsibility of developing autonomy regarding the self-management of their condition. Hanas suggests that parents should continue to take part in their child's diabetes care into adolescence and not hand the responsibility to the young person too early. Snoek and Skinner suggest that intensive self-management of diabetes is complex and time-consuming and creates a significant psychosocial burden on children and their families.

There are significant challenges for CYP to engage in effective diabetes self-management. Several of these were identified with Max and her mother:

- Deterioration in diabetes control.
- Difficulty with carbohydrate counting.
- Insulin omission.
- Fear of hypoglycaemia.
- Painful injections.

Action plan

An action plan was discussed between Max and the MDT. As she was on an MDI regimen (a long-acting insulin at bedtime and rapid-acting insulin with meals), a bolus advisor/blood glucose monitor was demonstrated and discussed with her and her mum.

Max felt she would be able to use this to help eliminate the calculations which, although she was capable of doing them, she often lacked time to do so. With further discussion, Max said she was "scared of getting it wrong and having a hypo". Insulin pump therapy was discussed but she did not want to "have a device attached to my body because it would remind me all the time that I have diabetes". Insulin pump therapy is recommended as a treatment option for adults and children over 12 years of age with type 1 diabetes whose HbA_{1c} levels remain above 69 mmol/mol (8.5%) on MDI therapy despite a high level of care.

The National Service Framework standard recommends empowering people with diabetes and encourages them and their carers to gain the knowledge and skills to be partners in decision-making and giving them more personal control over the day-to-day management of their diabetes, ensuring the best possible quality of life. However, if a diabetes management plan is discussed in partnership with a (Gillick-competent) young person but they elect not to comply with the plan despite full awareness of the implications of their actions, then the diabetes team should support them whilst trying to encourage them to maintain the treatment plan. This can be very difficult and frustrating at times, as a healthcare professional is an advocate for the patient, and promotion of the best interests of the patient is paramount.

Psychology involvement

Max was reviewed by the psychologist to assess her psychological health and wellbeing. The psychologist used the Wellbeing in Diabetes questionnaire (available from the Yorkshire and Humber Pediatric Diabetes Network) to assess her and identify an optimal plan of care.

The psychology sessions were focused on her issues around the following:

- Fear of hypoglycemia.
- Worry about deterioration in control.
- The consequences of insulin omission.
- Painful injections.

Max had a series of one-to-one appointments and some joint sessions with the pediatric diabetes specialist nurse and/or dietitian, so this linked into other team members' specialties.

Carbohydrate counting and use of a bolus advisor

The dietitian assessed Max and her mother's ability to carbohydrate count using a calculator, food diagrams and portion sizes, and both were able to demonstrate competency in this task. Garg et al have shown that the use of automated bolus advisors is safe and effective in reducing postprandial glucose excursions and improving overall glycemic control. However, this can only be true if the bolus advisor is being used correctly and is confirmed as such by comparing blood glucose and HbA_{1c} results before and after initiation of the bolus advisor, and observing the patient using the device to ensure it is being used safely and correctly.

Barnard and Parkin propose that, as long as safety and lifestyle are taken into consideration, advanced technology will benefit CYP, as inaccurate bolus calculation can lead to persistent poor diabetes control. These tools can help with removing the burden of such complex maths and have the potential to significantly improve glycemic control.

Insulin omission and fear of hypoglycemia

Max also expressed her fear of hypoglycemia and of "looking stupid" in front of her friends. She admitted to missing some of her injections, especially at school. Wild et a suggest that a debilitating fear of hypoglycemia can result in poor adherence to insulin regimens and subsequent poor metabolic control.

Crow et al describe the deliberate omission or reduced administration of insulin, which results in hyperglycemia and subsequent rapid reduction in body weight. Type 1 diabetes predisposes a person to a high BMI. Adolescent girls and adult women with type 1 diabetes generally have higher BMI values than their peers without the condition (Domargård et al,. Affenito et al () observed that insulin misuse was the most common method of weight control used by young women with type 1 diabetes. However, Max's weight remained stable and there was no clinical indication that she was missing insulin to lose weight; rather, it was her fear of hypoglycemia that drove her to omitting insulin at school. With the use of the bolus calculator, she was reassured about her calculations for insulin-to-carbohydrate ratios, but it was reinforced with her that the device would only work efficiently if she used it correctly with each meal.

Painful injections

Max also highlighted that her injections were now more painful than when she was first diagnosed, and this was causing her distress each time she had to inject. Injection technique was discussed with her and demonstrated using an injection model, and her injection technique was observed and appeared satisfactory. She was using 5-mm insulin needles and so was switched to 4-mm needles, as recommended by Forum for Injection Technique guidelines.

Appropriate technique when giving injections is key to optimal blood glucose control; however, evidence suggests that injection technique is often imperfect. Studies by Strauss et al and Frid et al revealed disturbing practices in relation to injection technique, with little improvement over the years.

Current diabetes guidelines do not include detailed advice on injection techniques, and only the guidance on type 2 diabetes in adults makes any reference to providing education about injectable devices for people with diabetes. However, the older Quality Standard for diabetes in adults recommends a structured program of education, including injection site selection and care.

Conclusion

The issues and concerns this young girl had been identified and addressed by the diabetes MDT. She was assessed by several members of the team, and a credible, evidence-based action plan was put into place to assist her and her mother to manage her diabetes at this difficult time. Max is now using the bolus advisor confidently and having fewer hypoglycemic episodes, and her HbA_{1c} has improved. She prefers using the 4-mm injection pen needles, although she remains hesitant when giving injections; she will still not consider insulin pump therapy. Her one-to-one sessions with the psychologist have now ceased, but she is aware she can access a psychologist at clinic on request, or if the MDT assesses that her psychological health has deteriorated.

When a child in a family develops a chronic condition, such as type 1 diabetes, effective communication is vitally important to address issues with the family at the earliest stage so that problems can be discussed and, hopefully, resolved before they escalate out of control. Upon reflection, the team could have become more intensely involved at an earlier stage to prevent Max's diabetes management issues and stop her HbA_{1c} from reaching such a high level. Furthermore, the new guideline has set the target HbA_{1c} at ≤48 mmol/mol (6.5%), so there is still some work to be done. However, the outcome of this case appears to be favorable at present.

Case Study 3

Patient Profile

The patient in question is a 46-year-old Caucasian female who is married with two high school-aged children. She is 5 feet, 3 inches tall and weighs 225 pounds. Over the past five years, TP has gradually gained weight and is now well above her ideal weight of 130 pounds. She does not partake in a healthy diet and eats many of her meals on the go. She also does not exercise on a regular basis and often experiences fatigue. Both of TP's pregnancies were difficult and had minor complications during birth. TP also experienced post-partum depression with both of her children and has periods of mood swings. She works outside of the home and volunteers at her children's high school on the PTA. She is often on the go and finds it difficult to maintain a healthy diet. As a result, her weight has increased dramatically over the past several years.
Patient History and Clinical Course

Laboratory Data

The patient first presented at the emergency room with lethargy, fatigue, excessive thirst, and frequent urination. She had become severely dizzy at home and was unable to regain her balance and stand on her own. Her husband suggested that she should be taken to the emergency department for further evaluation. Upon initial examination, her initial blood sugar level upon testing was 205 mg/dL, which was cause for immediate concern. Upon additional testing at fasting, her blood sugar level was 175, which remained high, with diabetes as the primary suspected cause. During her stay in the emergency department, TP's dizziness subsided, and she began to regain full balance and awareness of her surroundings.

Investigations

Upon physical examination and vital signs, the physician noted that TP was severely overweight. Her blood pressure was 165/100 upon measurement. The physician was concerned that a combination of elevated blood pressure and diabetes-related symptoms was highly problematic for TP and likely contributed to her recent dizzy spell. Therefore, she was diagnosed with diabetes and hypertension at the time of the visit. The physician was required to make decisions regarding the course of her care and treatment plan so that she would be able to better manage her symptoms and related complications.

However, the physician was concerned regarding her dizziness and as a precaution, ordered additional testing to ensure that there were no underlying neurological complications. Therefore, she was admitted to the hospital overnight for observation and for further testing.

Medication

The physician in charge of TP's case was required to make a number of decisions regarding the administration of medications to treat the diabetic condition. TP had been notified of her diagnoses and the risks associated with these conditions. Therefore, the physician prescribed an oral medication to determine if TP would respond to this first line of defense and if it would be effective in regulating her blood sugar levels. TP was prescribed Metformin (Glucophage) 500mg BID and Lisinopril (Zestril) 10 mg BID to determine whether or not the patient would respond favorably to this treatment regimen.

Treatment from Admission to Transfer of Care

Upon the decision to admit TP overnight, it was important to administer the recommended medications to ensure that her diabetes and hypertension began to regulate as quickly as possible. This was an important step towards the discovery of new insights regarding the patient and her ability to tolerate the medication and to determine if it would be effective over the long term. It was important for the patient to begin pharmacological treatment as quickly as possible to prevent further complications from her excessive blood pressure and blood sugar levels. Therefore, she was administered the first dose of each medication in the emergency department while waiting to be transferred to the medical unit for overnight observation and long-term management of these conditions. TP recognized the severity of her condition and accepted the physician's recommendations because she sought to improve her own health and to feel better on a daily basis, which she had not experienced for quite some time.

Care Plan During Admission: Patient Goals and Outcomes

Upon review of TP's current symptoms and presentation, it was important to identify both a short and long-term treatment strategy so that her symptoms would not only improve, but she would also experience significant benefits from medication administration as well as lifestyle changes. It was important to identify the challenges associated with her condition but to also recognize that they were treatable and manageable. Upon review of TP's case and the decision to admit her overnight for testing and observation, it was determined that her level of comfort and level of knowledge regarding her health status were of critical importance.

Prior to her visit to the emergency department, TP had recognized that her health was suspect; however, she had chosen to ignore some of the warning signs and did not take any precautions or other steps to improve her health and wellbeing through lifestyle changes. Therefore, in addition to establishing a medication-based treatment plan, the patient would be required to obtain additional education regarding her condition and how to best manage it through a combination of medication administration and lifestyle changes.
The latter would serve as the primary focus of the educational component of her treatment plan to lose weight, consume a healthier diet, and exercise regularly.

Assessment of Body Systems Influencing Diabetes

Diabetes has several significant impacts on organs and systems if left uncontrolled or undiagnosed for long periods of time. In addition, for those patients who are able to manage their diabetes effectively, organ and system damage may also occur. From a cardiac perspective, diabetes is perhaps one of the most important contributors to the diagnosis of hypertension and is likely the reason behind TP's own diagnosis. Furthermore, patients with diabetes are more likely to experience a greater risk of cardiovascular disease in different forms (diabetes.co.uk). In this context, patients must be observed regularly to identify any possible cardiovascular complications as a result of the diabetic condition. In addition, diabetes is a precursor in increasing the risk of stroke. Over time, diabetes has a significant impact on eye function, including a greater risk of diabetic retinopathy, particularly when diabetes is uncontrolled. Kidney function may also decline with diabetes and may lead to diabetic nephropathy. Diabetes has a significant impact on nerve function throughout the body, particularly in the hands and feet, and may lead to numbness and tingling, as well as the development of diabetic neuropathy.

Under these conditions, it is important to identify the challenges associated with managing diabetes effectively as early as possible so that long-term damage is minimized for this patient population to prevent serious complications.

Discussion

It is important to diagnose diabetes as early as possible so that treatment may begin, and long-term complications and organ/system damage may be reduced. In supporting the educational strategy for TP, it was important to utilize the services of an advanced practice nurse (APN) to support the treatment plan and long-term management program.

In this capacity, “At the completion of assessments, advanced practice nurses, in conjunction with patients, identify management goals and determine appropriate plans of care. A review of patients’ self-care management skills and application/adaptation to lifestyle is incorporated in initial histories, physical exams, and plans of care”. Therefore, it is important for patients to be provided with a strategy or plan of care that will be most effective in meeting their specific needs associated with diabetes management to promote the desired outcome. It is important for APNs and other clinical knowledge experts to provide guidance and insight as necessary to ensure that patient outcomes are accomplished and met on a continuous basis. It is not sufficient to provide initial education and then fail to continue to provide guidance on a routine basis; rather, patients such as TP must be evaluated and monitored consistently to determine how to best move forward in the chosen treatment plan.

Key Outcomes

In the example case study involving TP, it was important to identify the challenges associated with her diagnosis and plan of care over the long term. TP’s diabetes had progressed for a period of years and had gone undiagnosed. However, the physician and clinical team believed that she could maintain her health and minimize damage by taking her medication as required and conducting several important lifestyle changes in her personal life.

The physician recommended that TP establish a healthy nutrition plan and exercise regimen to reduce her weight on a gradual basis. TP took these recommendations seriously and joined a local Weight Watchers group to assist her with her weight loss goals.

She began with small yet gradual changes to her diet, replacing some carbohydrates with vegetables and reducing her meat intake. She quit drinking soda altogether and also reduced her intake of sweets. She also began walking three times per week and gradually increased it to six days per week, four miles per day.

Over a period of nine months, TP lost 65 pounds and was on her way to achieving her weight loss goal of 95 pounds.

She had achieved her goals and now had a new lifestyle to show for it. As a result, TP’s diabetes was under control and her blood sugar levels were almost consistently in the proper range. In addition, her blood pressure was under control and her medication levels were reduced. She continued to see her physician every few months to determine if there were any other required changes to her medication schedule. TP was on the right track to successful outcomes and sought to be as successful as possible in her lifestyle regimen to eventually be permitted to manage her diabetes without medication and solely with proper diet and exercise.

What Was Learned

With this example case study, it became evident that diabetes is a very serious and debilitating condition that causes widespread damage to organs and systems if left untreated. Therefore, this condition requires immediate diagnosis, care, and treatment to ensure that it is managed properly and effectively. This is an important step towards the development of new strategies to reduce diabetes-related complications and symptoms and to focus on prevention as best as possible. In this example, TP recognized that her health was in decline, but was perhaps fearful of the outcomes. Therefore, she did not obtain treatment until she had no other choice. This is not the most ideal means of managing this type of condition, as it should be diagnosed and treated as quickly as possible to prevent further complications and other long-term damage to body organs and systems.
It is imperative that individuals recognize that when symptoms arise that are typical of diabetes, immediate guidance and treatment are essential to the long-term care plan for these patients.

What Should Readers Learn

Based upon the results of this case study, it is important for readers to recognize the necessity of being proactive rather than reactive in diagnosing, treating, and managing diabetes over the long term. These efforts require a greater understanding of diabetes and its impact on organs and systems, as well as the importance of diabetes-related education and a proper treatment plan. This case study example provides further evidence of the dangers of excess weight and obesity on the body and how poor diet and limited exercise play a role in increasing the risk of diabetes and related complications.

Therefore, nurses and other clinical staff members must be prepared to work with diabetes patients and possess the knowledge that is necessary to improve outcomes and to reduce these risks over time. These efforts will demonstrate that diabetes should be always taken seriously under all conditions and that there are significant benefits to establishing a treatment plan and lifestyle changes to reduce the long-term impacts of this condition.

Conclusion

Diabetes is a highly challenging and complex condition that requires significant attention and focus in order to reduce its symptoms and long-term complications. In this context, it is necessary for patients to recognize when they might have some of the symptoms of diabetes and to seek guidance and treatment from their physician.

These efforts require a greater understanding of diabetes and its impact on organs and systems because these impacts may ultimately reduce the quality of life for these patients. Therefore, it is important to identify methods of reducing the risks of diabetes at the prevention stage so that there are fewer diagnoses of this condition in the general population. With this framework in mind, diabetes-related education is critical to prevention and in enabling population groups to recognize their own risks and how to prevent these risks from leading to a diagnosis of diabetes. It is imperative that clinical professionals work with patients such at TP to recognize these risks and to begin treatment as necessary when a diagnosis is made. This will enable clinicians to be effective in addressing the severity of diabetes and its potential impact on patient care and wellbeing for many patients.

Chapter 4: Diagnostic Criteria and Methods

Accurate diagnosis of diabetes is crucial for effective management and prevention of complications. Diagnostic criteria and methods have evolved over time, with advances in technology improving the accuracy and ease of diagnosis.

Evolution of Diagnostic Criteria

Diagnostic criteria for diabetes have changed significantly over the years to improve accuracy and early detection.

Historical Perspective:

The diagnostic criteria for diabetes mellitus have evolved over time, taking into account new evidence. Here, we review the evolution of diagnostic criteria for diabetes mellitus, the current diagnostic criteria, and future perspectives. Current Concepts: For the first time, in 1965, the World Health Organization (WHO) recommended that a 2-hour plasma glucose concentration of 130 mg/dL or more after taking a 50-g or 100-g oral glucose bolus may be used to make the diagnosis in people younger than 45 years and that other clinical data might be used to make the diagnosis in people older than 45 years. The 2003 American Diabetes Association Diagnostic Criteria set the threshold for normal fasting glucose at 100 mg/dL

> The International Expert Committee (IEC) in 2009, the American Diabetes Association in 2010, and the WHO in 2011 proposed new diagnostic criteria for diabetes: glycated hemoglobin (HbA1c) of 6.5% or higher. More recently, diabetes has been diagnosed via a fasting blood glucose of 126 mg/dL or higher after fasting for at least 8 hours, a 2-hour postprandial blood glucose of 200 mg/dL or higher, glycated hemoglobin of 6.5% or higher, or a random blood glucose of 200 mg/dL or higher with symptoms of hyperglycemia.

Discussion and Conclusion: Further research is needed on the accuracy of other markers, such as HbA1c, fructosamine, and 1,5-anhydroglusitol, in the diagnosis of diabetes, and sufficient evidence is required to determine whether it is appropriate to use the same diagnostic criteria for diabetes in aged people and different ethnic groups.

- Early diagnostic criteria were based on symptoms such as excessive thirst and urination. Blood glucose testing became the standard in the 20th century.

Current Standards: The American Diabetes Association (ADA) and the World Health Organization (WHO) have established guidelines for diagnosing diabetes. These include fasting plasma glucose (FPG), oral glucose tolerance test (OGTT), and hemoglobin A1c (HbA1c) levels.

Current Diagnostic Methods

Several methods are currently used to diagnose diabetes, each with their advantages and limitations.

- **Fasting Plasma Glucose (FPG):** Measures blood glucose levels after an overnight fast. A level of 126 mg/dL (7.0 mmol/L) or higher indicates diabetes.

The FPG test is recommended as a screening test for people 35 or older to be repeated every three years. It may also be used for people who have symptoms of diabetes or multiple risk factors for diabetes.[1]

Fasting for several hours triggers a hormone called glucagon, which is produced by the pancreas and causes the liver to release glucose (blood sugar) into the bloodstream.[2]

- If you don't have diabetes, your body reacts by producing insulin, which prevents hyperglycemia (high blood sugar).
- If your body cannot generate enough insulin or cannot appropriately respond to insulin, fasting blood sugar levels will stay high.

- **Oral Glucose Tolerance Test (OGTT):** Measures blood glucose levels before and two hours after consuming a glucose-rich drink. A two-hour blood glucose level of 200 mg/dL (11.1 mmol/L) or higher indicates diabetes.

The oral glucose tolerance test shows how well your body deals with the sugar (glucose) after a meal. Glucose is a type of sugar that is made when the body breaks down carbohydrates from the food that you eat. Some of the glucose will be used for energy and the rest is stored to use later.

The amount of glucose in your blood is controlled by the hormones insulin and glucagon. If you have too much glucose in your blood, your pancreas puts out (secretes) insulin to help cells absorb and store it.

If you have too little blood sugar, the pancreas secretes glucagon to release the stored glucose back into your bloodstream.

The body is usually able to maintain the ideal balance of blood glucose. However, if any parts of the system do not work, glucose can build up fast and lead to high blood sugar levels (hyperglycemia) and diabetes.

The oral glucose tolerance test can spot imbalances in this process that other tests can miss. The National Institute of Diabetes and Digestive and Kidney Diseases (NIDDK) recommends that the oral glucose tolerance test be used for:

- Screening and diagnosis of prediabetes or impaired glucose tolerance (IGT)
- Screening and diagnosis of type 2 diabetes
- Screening and diagnosis of gestational diabetes[2]

The oral glucose tolerance test can also be used to diagnose:

- Reactive hypoglycemia (when blood sugar drops after eating)
- Acromegaly (an overactive pituitary gland)
- Beta cell dysfunction (when insulin is not being secreted)
- Rare disorders that affect carbohydrate metabolism (e.g. hereditary fructose intolerance)

- **Hemoglobin A1c (HbA1c):** Reflects average blood glucose levels over the past two to three months. An HbA1c level of 6.5% or higher indicates diabetes.

Hemoglobin A, a protein found inside red blood cells, carries oxygen throughout your body. When there's glucose in your bloodstream, it can stick (glycate) to hemoglobin A. The more glucose that's in your blood, the more it does this, creating a higher percentage of glycated hemoglobin proteins.

Once glucose sticks to a hemoglobin protein, it typically remains there for the lifespan of the hemoglobin A protein (as long as 120 days). This means that, at any moment, the glucose attached to the hemoglobin A protein reflects the level of your blood sugar over the last two to three months.[1]

The A1C test measures how much glucose is actually stuck to hemoglobin A, or more specifically, what percentage of hemoglobin proteins are glycated. Hemoglobin with glucose attached to it is called A1C. Thus, having a 7% A1C means that 7% of your hemoglobin proteins are glycated.

Depending on why the healthcare provider is ordering the test, the blood sample may be obtained from either a regular blood draw or by pricking your finger with a lancet.

The healthcare provider may order an A1C test for the following reasons.

Screening for Diabetes

If you're overweight or obese and you have one or more other risk factors for developing type 2 diabetes, your healthcare provider will likely order an A1C test (or another diabetes test) as part of your annual medical exam.

Such risk factors include:

- A parent or sibling with diabetes
- Being physically inactive
- High blood pressure
- High triglycerides
- Low HDL cholesterol
- A history of cardiovascular disease
- High-risk ethnicity (Native American, African American, Latino, Asian American, Pacific Islander)
- Having conditions associated with insulin resistance, including acanthosis nigricans, severe obesity, or polycystic ovary syndrome (PCOS)

- **Random Plasma Glucose Test:** Measures blood glucose levels at any time of the day, without fasting. A level of 200 mg/dL (11.1 mmol/L) or higher, along with symptoms of diabetes, indicates diabetes.

A random glucose test, also known as a random blood glucose test (RBG test) or a casual blood glucose test (CBG test) is a glucose test (test of blood sugar level) on the blood of a non-fasting person. This test assumes a recent meal and therefore has higher reference values than the fasting blood glucose (FBG) test.

Emerging Diagnostic Technologies & Technology Innovations

Advances in technology are leading to new and improved methods for diagnosing diabetes.

- **Continuous Glucose Monitoring (CGM):** Provides real-time data on blood glucose levels, helping to identify trends and patterns.

These systems are made up of three components: the sensor (a small wire catheter that is inserted under the skin on your arm or abdomen), a transmitter that attaches to the sensor, and a handheld receiver and/or smartphone that displays your glucose data in real time.

The Pros

1. Offers alerts. The most significant benefit of all real-time CGM systems is having audible alarms that can warn you if your blood sugar (blood glucose) is getting too high. This allows time for adjustments that could lessen the impact of high or low blood sugar or avoid it altogether.
2. Transmits data continuously. With real-time CGM devices, data is constantly pushed to a receiver or smartphone without the need for additional action, such as a finger prick.
3. Shares data. The ability to share data with family members and friends is another important feature. It acts as a safety net, especially when traveling. For example, if you don't wake up to a low glucose alarm during the night, someone else will be alerted and can get in touch with you.
4. Eliminates finger sticks. While not all real-time CGMs offer this benefit, some allow you to make treatment decisions—how much insulin to dose, for instance—without the need for finger-stick confirmation. Plus, some are factory calibrated, eliminating the hassle and pain of calibrating with finger sticks.

The Cons

1. Requires setup. To use the alarm and alert features, you have to program your settings, such as your low glucose threshold and target ranges. This can get a little complicated, especially if you don't read the instructions. However, the manufacturers offer online video tutorials to guide you through the process. Your diabetes care team, particularly your diabetes educator, can help you learn to use your device.
2. Alerts can be tiresome. Some people complain about the repeated alarms (real or false). It can become so bothersome—or embarrassing, depending on where you are or who you're with—that they simply turn off the alarms altogether. However, this is mainly a problem with the older CGM systems, which are not as accurate as the newer ones.
3. Devices can be expensive. Although they are covered by most insurance companies and Medicare, they may not be affordable if you have to pay out of pocket. If cost is an issue, know that many device manufacturers offer patient assistance programs

- **Wearable Devices:** Emerging wearable devices can monitor blood glucose levels non-invasively, offering a more convenient option for patients.

- When the Medtronic MiniMed™ 502 came out in 1983, many people thought the golden age of diabetes tech was upon us.
- It's an understatement to say that we've come a long way in the last 40 years. I believe we are *now* in the golden age of diabetes tech (although I'm sure in another 40 years they will be saying the same thing).
- Still, despite all the innovative diabetes digital health tech that's out there, we experience the antiquated notion that "tech is for the type 1s" on a regular basis. Today's tech tools should be considered for appropriate people looking to manage their diabetes, regardless of type.
- Here are the 5 pieces of tech we think every primary care practice should be considering for their appropriate patients with diabetes. For this article, I'll focus primarily on tech for people taking insulin.

Diabetes Management Apps

It's rare these days for me to come across a fellow person with diabetes who doesn't have a smartphone. I see diabetes management apps as a great "gateway tech." For anyone already using a smartphone, installing a new app is something they're generally familiar with. In my experience, once they see how the app works and how technology can help them in their diabetes care, it may help them open up to other types of tech.

Some of today's apps sync with CGMs, connected insulin pens/pen caps, and insulin pumps (all of which I'll discuss shortly), and they allow people to track other lifestyle factors that impact their diabetes, such as eating patterns and physical activity.

When a patient shares diabetes data from the app with their care team, it can help give providers a clearer picture of that person's condition to help inform treatment decisions and better conversations.

Continuous Glucose Monitors

CGMs continuously monitor interstitial glucose levels throughout the day and night through a sensor inserted subcutaneously into the skin.

Wearing a bulky CGM can be a barrier for people who don't want to draw attention to their condition, but today's CGMs are much smaller and more discreet than their predecessors.

Today's CGMs also offer a variety of special features, depending on the model. For example, if a child's glucose drops dangerously low overnight, some CGMs can send an alert to wake a parent in another room.

When paired with a smart insulin pen or pump, providers can also get a better picture through the person's ambulatory glucose profile (AGP) report, which includes "time in range" and how ups and downs in glucose are affected by insulin doses, meals, time of day, etc. I've found that many people with diabetes are striving for improved glucose control but struggle with the hassle of logging their glucose levels manually. CGMs automatically provide useful logs, which can be shared with health care providers to help uncover areas where patients could potentially make changes.

Smart Insulin Pumps

Today's insulin pumps not only do what they've always done (deliver small doses of insulin continuously at a basal rate or as bolus doses before meals to help control glucose levels), but they also record all this data so it can help inform patients and providers alike.

Like smart insulin pens and pen caps, smart insulin pumps can sync with diabetes management apps and CGMs to help form a clearer picture of what's affecting glucose levels throughout a typical day.

Today's insulin pumps are small, discreet, and some also offer tubeless technology, which has helped many people I know get over the hump and give a pump a try.

Smart insulin pens and connected pen caps

For people with diabetes who don't want to wear a pump but could benefit from automated insulin dose logging, smart/connected insulin pens and pen caps may also be an option. These devices have a sensor to record the date, time, and dosage of insulin injections so people don't have to track their doses manually in a logbook.

All that data then gets wirelessly and securely transferred to a compatible diabetes management app and can be shared with health care providers.

When insulin dose and administration data is paired with glucose data collected via CGM, providers can assess the information and determine if any adjustments need to be made to the individual's insulin routine.

Automated Insulin Delivery (AID) systems

Formerly called "artificial pancreas" technology, new AID systems may be beneficial for people with diabetes who are insulin dependent. Many companies and individual innovators are developing versions of AID; the systems are still evolving and not available to everyone yet, but the technology is on the horizon to make them more widely accessible.

An AID system is a combination of a CGM, a control algorithm that analyzes the data and calculates the required insulin dose, and a smart insulin pump that communicate with each other wirelessly, creating a "closed loop" that mimics what a healthy pancreas does. The system monitors glucose levels and delivers appropriate insulin doses throughout the day and night.

The CGM checks the patient's glucose level, the algorithm determines if and when an insulin dose is needed, and the pump delivers the right dose at the right time—in an ideal version of the closed-loop system, it's completely autonomous. And of course, as is the theme with today's diabetes tech, the device captures the glucose level and insulin dosing data to help inform the patient and health care provider.

While the potential benefits are obvious, for now, AID systems require people with diabetes to wear two separate pieces of tech (the CGM and the pump). This may be a dealbreaker for some, but we are excited to see how this tech evolves in the future.

- **Genetic Testing:** Identifies individuals at high risk for diabetes based on their genetic profile, allowing for early intervention and personalized treatment plans.

Genetic testing can be used to identify certain forms of diabetes that are monogenic, meaning that they are related to a change or defect in a single gene. Both neonatal diabetes and MODY are monogenic, and both tend to be incorrectly diagnosed.[13]

Genetic testing is important for making a precise diagnosis, particularly for these monogenic types of diabetes. Furthermore, without a correct diagnosis, the affected person cannot get the proper treatment for the type of diabetes they have.

Physicians often recommend genetic testing when a diabetes diagnosis appears to be atypical. For example, a person who is around age 20 to 25, has abnormal blood sugars, and who does not have any typical risk factors for type 1 or type 2 diabetes, may have MODY.

Genetic diagnosis of MODY additionally allows for the identification of at-risk first-degree family members, who have a 50% chance of inheriting a gene mutation.

Unfortunately, insurance often denies coverage for genetic testing even when people fit the criteria, which can cause physicians to miss a MODY diagnosis. Researchers are continually trying to find ways to make genetic testing more cost-effective.

The screening is free for relatives of people with type 1 diabetes. It uses a blood test to detect diabetes-related antibodies, the presence of which means that the immune system has begun to attack cells in the pancreas. The screening can detect these antibodies years before diabetes symptoms even begin.

People found to be in the early stages of developing type 1 diabetes may also be eligible for the prevention study. Ask your healthcare provider whether genetic testing is available and how helpful it is in determining if you will get diabetes.

Whereas MODY and neonatal diabetes are monogenic, diabetes type 1 and type 2 are polygenic, meaning they are related to changes in multiple genes.

Currently, researchers do not feel that genetic testing is ready to diagnose type 2 diabetes. Because there are so many variants of genes and subtypes of type 2 diabetes, they feel as though better methods and more research need to be done in this area before putting it to practical use.

- **Biomarker Analysis:** Research is ongoing to identify new biomarkers that could improve the accuracy of diabetes diagnosis and predict the risk of complications.

In simple words, biomarkers (short for biology markers) are the measurable characteristics of the body that relay vital information about its health status. This is a biomolecule found in the blood, bodily fluids, or tissues that is an indicative sign of good health, health conditions, or diseases. Body temperature, blood sugar level, blood pressure, body mass index (BMI), and heart rate are some of the biomarkers that can tell you what's going on with someone's health. For instance, high cholesterol levels are a common biomarker for heart disease risk. Similarly, high blood glucose levels indicate prediabetes or diabetes.

The most significant aspect of biomarkers is that they can act as an early warning system for any kind of disruption in your body. Their role is of further importance when it comes to personalized medical care. They indicate how competently or incompetently your body is reacting to a line of treatment, which allows your healthcare provider to make modifications to the treatment plan.

Biomarkers for diabetes reveal the presence and severity of hyperglycemia or the presence and severity of vascular complications of diabetes. Elevated blood glucose level, hypoglycemia, elevated blood pressure, low HDL cholesterol, and elevated triglycerides are some of the common biomarkers of diabetes. HbA1c (hemoglobin A1c) is the most prominently used biomarker to detect hyperglycemia. Apart from that, testing is also done using a fasting blood sugar test or random blood sugar test to detect the glucose level in the bloodstream. These tests indicate a person's diabetic diagnosis.

How Do You Measure Them?

HbA1c

HbA1c (glycated hemoglobin) test indicates a person's average blood sugar level for the past 2-3 months. The purpose is to diagnose the diabetic stage (whether prediabetes or not), whether type 1 or type 2 diabetes, and to monitor the effectiveness of your line of treatment. If you are diagnosed with prediabetes, you have a higher risk of developing diabetes and cardiovascular disease.

Following is the range in which the result of the HbA1c test is interpreted as

- Below 5.7% is normal.
- 5.7% to 6.4% are diagnosed with prediabetes.
- 6.5% or higher on two separate tests indicates diabetes.

Fasting Blood Sugar Test

As the name suggests, a blood sample is taken after an overnight fast in this test. The result is interpreted as the amount of sugar per unit of blood and is diagnosed as per the following:

- Less than 100 mg/dL (5.6 mmol/L*) is normal.
- 100 to 125 mg/dL (5.6 to 6.9 mmol/L*) is diagnosed as prediabetes.
- 126 mg/dL (7 mmol/L*) or higher on two separate tests is diagnosed as diabetes.

Note: mmol/L is millimoles of sugar per liter of blood.

Random Blood Sugar Test

A blood sugar level of 200 mg/dL (11.1 mmol/L) or higher suggests diabetes, regardless of the time you ate your last meal, especially if you show symptoms like frequent urination, increased hunger, and thirst.

What is the Ideal Frequency of Doing These Tests?

The frequency of getting an HbA1c test done depends upon your risk factors, blood glucose levels, and your treatment routine. It is always a good idea to get an annual HbA1c test done if you have prediabetes. With type 2 diabetes, a minimum of twice a year works well, given that you are not on insulin and keep your blood glucose levels regulated. For those type 2 diabetics who do take insulin and are not able to manage their blood sugar within their target range, it is a good idea to get the HBA1c test done four times a year. This frequency may further vary if your doctor changes your treatment plan or alters your medication dose.

Most people with type 2 people have their blood sugar target range below 7%. Now, to achieve this target, one needs to maintain a self-monitoring routine with the help of a glucometer. Self-measured glucose levels usefully complement hemoglobin A1c levels to guide daily management decisions. So, for instance, if your A1C target is below 7%, your blood sugar levels, on average, should be below 154 mg/dL (8.6 mmol/L).

For any other range worked out by your doctor, consider the following table:

HbA1c level	Estimated average blood sugar (glucose) level
6%	126 mg/dL (7 mmol/L)
7%	154 mg/dL (8.6 mmol/L)
8%	183 mg/dL (10.2 mmol/L)
9%	212 mg/dL (11.8 mmol/L)
10%	240 mg/dL (13.4 mmol/L)
11%	269 mg/dL (14.9 mmol/L)
12%	298 mg/dL (16.5 mmol/L)

- **Artificial Pancreas:** Closed-loop systems that combine CGM with insulin pumps to automatically regulate blood glucose levels, mimicking the function of a healthy pancreas.

Located in the abdomen behind the stomach and under the liver, the **pancreas** is a digestive organ that helps break down food and regulate blood glucose (sugar). Pancreatic enzymes help digest carbohydrates, fats, and proteins, while pancreatic hormones signal the need to increase or decrease blood sugar levels. The pancreas is divided into sections called the head, uncinate process, neck, body, and tail. The pancreas is closely associated with the duodenum (the first section of the small intestines) and gallbladder.

The **pancreatic duct** connects with the **common bile duct** from the gallbladder to form the **hepatopancreatic ampulla and sphincter.** This muscular channel controls the flow of digestive enzymes and drains directly into the duodenum. The **accessory pancreatic duct** provides additional drainage access to the duodenum, when the body eats food that contains carbohydrates, the blood sugar levels rise. In response, the pancreas sends insulin to help move glucose (sugar) from the blood to different cells within the body (muscle, fat, or liver) to be stored or used as energy. This causes blood sugar levels to lower.

An artificial pancreas, also known as an automated insulin-delivery (AID) system, hybrid closed-loop system, or bionic pancreas, is designed to mimic the work of a healthy pancreas to keep blood sugar levels from rising too high.

It automatically and frequently checks blood sugar levels day and night. Depending on the blood sugar level readings, the artificial pancreas system will adjust and deliver insulin doses via an insulin pump to bring blood sugar levels down and into a healthy range.[2]

An artificial pancreas is made up of three devices:

- A continuous glucose monitor (CGM) monitors blood glucose levels every few minutes using a tiny sensor inserted under the skin. The CGM sends the blood glucose level readings to a program installed on a smartphone or insulin pump.

- The controller, or computer program, takes the blood glucose readings and uses an algorithm (set of rules and problem-solving operations) to calculate how much insulin is needed to bring blood sugar levels back to the target range. It sends this information to the insulin pump.

- The insulin infusion pump adjusts and delivers small doses of insulin throughout the day in response to blood sugar levels.

- An artificial pancreas costs depends on insurance coverage and which closed-loop system you choose to purchase. Insurance might not cover all the costs of an AID system but may be able to significantly reduce the price. For example, some insurance companies will cover 80% of the cost, leaving you to pay 20%.
- Aside from the initial cost of purchasing a closed-loop system, the person will need to pay for an insulin pump and CGM supplies on an ongoing basis.
- An insulin pump costs about $6,000 without insurance.[7] Depending on which CGM you choose, the cost may be as low as $40 per month[8] with insurance.[9] However, even with insurance, the yearly cost of supplies for an AID system may be between $3,000 to $6,000 per year[7] or more if you don't have insurance.
- Most manufacturers have cost calculators on their website to help determine the cost depending on your insurance plan or if you are cash pay. Some manufacturers also offer free trials, coupons, savings programs, or financial assistance to help keep the costs down.

Stem Cell Research and Regenerative Medicine

Stem cell research holds promise for developing new treatments and potential cures for diabetes.

- **Beta-Cell Replacement:** Research is exploring the potential of stem cells to generate new insulin-producing beta cells, which could be transplanted into individuals with diabetes.

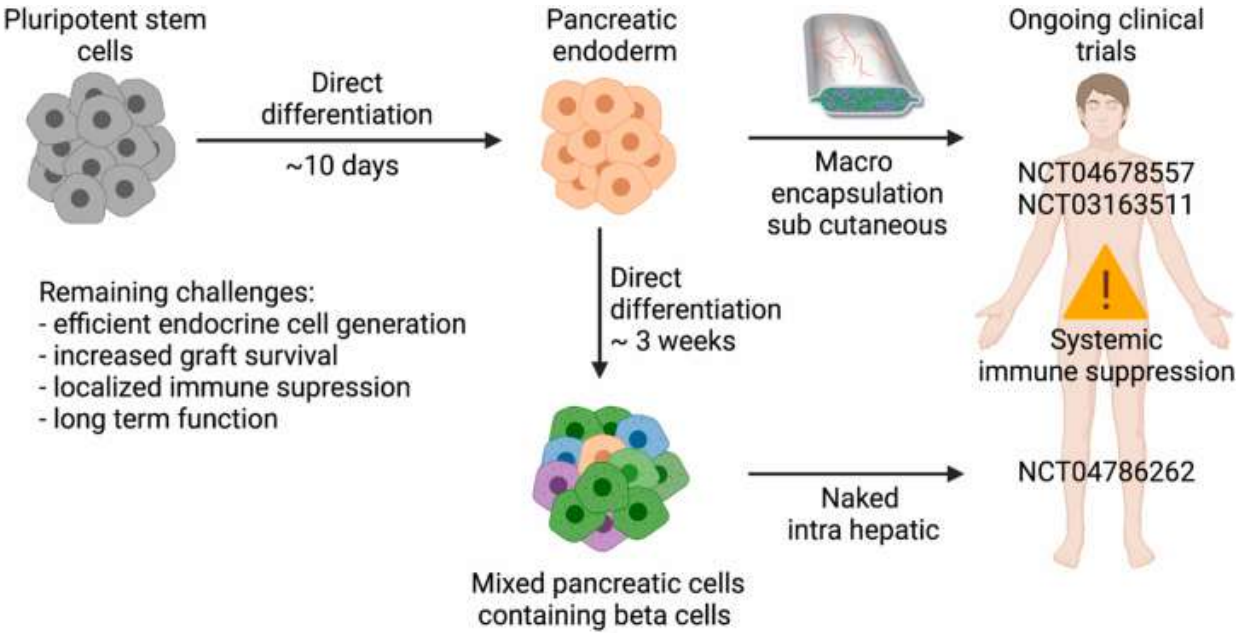
Stem cell therapies are finally coming of age as a viable alternative to pancreatic islet transplantation for the treatment of insulin-dependent diabetes. Several clinical trials using human embryonic stem cell (hESC)-derived β-like cells are currently underway, with encouraging preliminary results. Remaining challenges notwithstanding, these strategies are widely expected to reduce our reliance on human isolated islets for transplantation procedures, making cell therapies available to millions of diabetic patients. At the same time, advances in our understanding of pancreatic cell plasticity and the molecular mechanisms behind β-cell replication and regeneration have spawned a multitude of translational efforts aimed at inducing β-cell replenishment *in situ* through pharmacological means, thus circumventing the need for transplantation.

The last two decades have witnessed an unrelenting quest to create an unlimited supply of insulin-producing cells that could be transplanted in lieu of islets. Several cell sources that were actively explored throughout the early 2000s (e.g., mesenchymal, hematopoietic, fetal, xenogeneic, immortalized β-cell lines) are no longer a primary focus for the development of β-cell replacement therapies. Rather, the direct differentiation of human pluripotent stem cells (hPSCs) into pancreatic cell types has taken center stage. hPSCs come in two flavors: Embryonic stem cells (ESCs), which are derived from the inner cell mass of fertilized blastocysts not used in *in vitro* fertilization treatments; and induced pluripotent stem cells (iPSCs) generated by the reprogramming of somatic cells, a procurement method that circumvents the ethical concerns that hindered the use of ESCs. These two hPSC types share two main characteristics, namely, the capacity to divide rapidly in an undifferentiated fashion, and the ability to differentiate into virtually every cell type present in the body. While the promise of iPSC remains high in the context of personalized medicine, most translational advances described thus far have focused on the use of hESCs.

There are several ongoing clinical trials evaluating the safety and efficacy of either PE cells or sBCs (Figure 1). First-in-human trials were initiated by ViaCyte in 2014. The cellular product (VC-01TM/PEC-EncapTM) was largely composed of PE cells derived from the hESC line CyT49 macroencapsulated in an immunoisolation device, which was transplanted subcutaneously in fully immunocompetent patient.

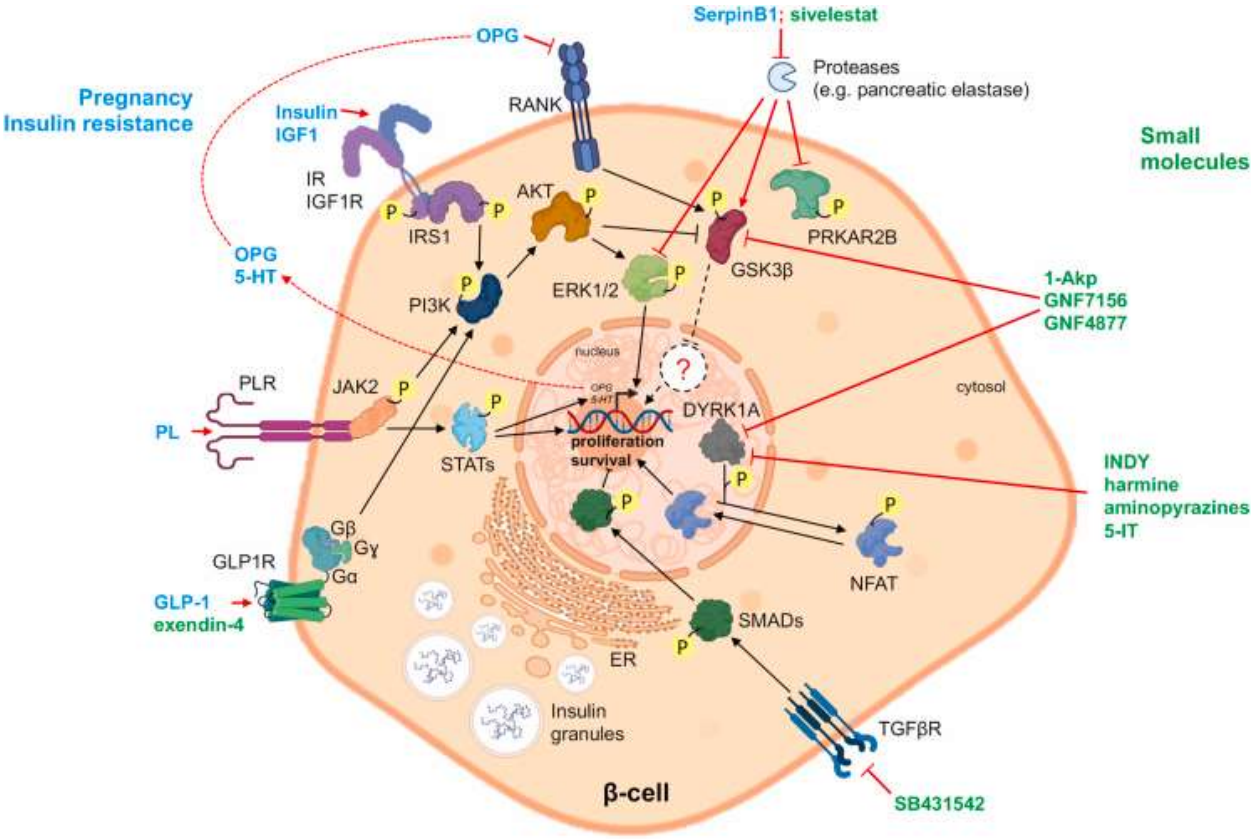
The device in question, an evolution of the Encaptra® drug delivery system, permits the exchange of nutrients and gas but prevents direct interaction with host immune cells, thus providing immune protection. The study, terminated in December 2017, showed that the treatment was safe and well tolerated, with no teratoma formation. The analysis of explanted sentinel devices demonstrated the *in vivo* generation of insulin-producing cells from PE cells after several months. However, the lack of direct interaction with the host vasculature, as well as a considerable foreign-body immune response to the device, reduced the exchange of oxygen and nutrients, negatively impacting the survival of transplanted cells. A phase II clinical trial with an optimized closed device is currently underway (ClinicalTrials.gov identifier: NCT04678557). Another embodiment of the device, containing pore openings at the surface that allow for the penetration of blood vessels, is also being tested with the same cells in Phase II clinical trials (ClinicalTrials.gov identifier: NCT03163511) [28,29]. While this approach provides better oxygenation and overall conditions for grafts, the need for systemic immune suppression is still problematic. Finally, ViaCyte and CRISPR Therapeutics just started a clinical trial with cells genetically engineered to evade detection by the immune system, which would also make use of the same porous version of the device (ClinicalTrials.gov identifier: NCT05210530).

Figure 1



Current clinical strategies for T1D based on hESC transplantation. Schematic depiction of the design of current clinical trials for T1D making use of hESCs. The first ones to be initiated and make use of partially differentiated hESCs (Pancreatic Endoderm, or PE) that are transplanted subcutaneously within a microencapsulation device. In (bottom), the cells are matured *in vitro* into functional glucose-responsive β-like cells (sBCs), which are subsequently transplanted naked (without immunoisolation device) intraportally with general immunosuppression of the recipient. Remaining challenges common to these approaches, further discussed in the main body of the article, include long-term function and survival of the graft, efficient generation of endocrine cells, and localized (vs. systemic) immunosuppression/immune evasion.

Figure 2



Molecular pathways controlling human β-cell proliferation. (Left, blue) Molecular mechanisms regulating β-cell growth to compensate for physiological (e.g. pregnancy) or pathophysiological (e.g. obesity, early onset T2D) increased insulin demand. During pregnancy, lactogenic hormones, such as prolactin are sensed by the prolactin receptor (PLR). PLR transduces the signaling downstream via the phosphatidylinositol-4,5-bisphosphate 3-kinase (PI3K)-AKT serine/threonine kinase (AKT) and the Janus kinase (JAK)-signal transducer and activator of transcription (STAT) axis, leading to the translocation of STAT proteins into the nucleus to initiate transcription of proliferative factors, including osteoprotegerin (OPG) and serotonin (5-HT). These molecules are then secreted in the islet milieu to sustain mitogenic signaling in an autocrine or paracrine fashion. OPG is known to increase survival of β-cells by blocking the interaction between the receptor activator of nuclear factor kappa-B (RANK) and its ligand (RANKL), avoiding the activation of glycogen synthase kinase-3β (GSK3β)-mediated intrinsic apoptotic pathways. In insulin resistance and pregnant states, circulating insulin and insulin-like growth factor 1 (IGF1) levels are elevated. Both growth factors regulate further expansion of β-cells binding the insulin (IR) and the IFG1 (IGF1R) receptors, resulting in the activation of the PI3K-AKT signaling. This, one the one hand, inhibits GSK3β; and, on the other, activates the extracellular signal-regulated kinase 1/2 (ERK1/2), which translocates into the nucleus to regulate gene expression.

Overt insulin resistance leads to the increase of serine protease inhibitor B1 (SerpinB1) in the liver and other tissues with metabolic regulation properties. SerpinB1 is then secreted into the circulation to dictate compensatory mechanisms at the islet level. SerpinB1 stimulates β-cell proliferation by blocking the activity of serine proteases (e.g. pancreatic elastase), resulting in the activation of ERK1 and protein kinase cAMP-dependent type II regulatory subunit β (PRKAR2B). (Right, green) Human β-cell proliferation can also be induced by exogenous treatment with small molecules. In particular, SerpinB1 effects are mimicked by elastase inhibitors (e.g. sivelestat). Moreover, chemical inhibitors of GSK3β, including GNF7156, GNF4877 or 1-Azakenpaullone (1-Akp) stimulate β-cell growth. The dual-specificity tyrosine-regulated kinase-1a (DYRK1A) inhibits β-cell regeneration by regulating the activity and localization of nuclear factor of activated T cells (NFAT), which is exported from the nucleus into the cytosol following phosphorylation. By suppressing the activity of DYRK1A using INDY, harmine, 5-iodotubericin (5-IT) or aminopyrazines, the non-phopshorylated form of NFAT remains in the nucleus to promote growth.

The transforming growth factor receptor (TGFβR) pathway inhibits proliferation via the activation of SMAD proteins that migrate into the nucleus to repress gene expression. This regulation can be interrupted by chemical inhibitors of TGFβR, such as SB431542, which induces β-cell regeneration. Although its role in regulating growth in human β-cells is the subject of active debate, the activation of glucagon-like peptide 1 receptor (GLP1R) by either GLP-1 or its analogues (e.g. exendin-4) triggers the PI3K-AKT pathway, following mobilization of the Gβ and Gɣ proteins. This figure was created using Biorender. (For interpretation of the references to color in this figure legend, the reader is referred to the Web version of this article.)

As for obesity, the reduction of insulin action in peripheral tissues leads to insulin resistance. To counteract this effect, β-cell mass expands to increase the circulating levels of insulin. This compensation has been quantified in non-diabetic obese patients as well as in mouse models of diet-induced obesity (HFD) and genetically-induced obesity (Ob/Ob) or insulin resistance (LIRKO) . Although the endogenous factors responsible for such regulation are yet to be identified, the potential mediation of circulating signaling molecules from other insulin-responsive tissues is an intriguing scenario. One of these may be leptin, a hormone produced by adipocytes that is mainly involved in the regulation of food intake. Serum leptin levels are increased in obese subjects and in rodent β-cells it has either a proliferative or an antiapoptotic effect. However, they translate poorly in human islet samples. Likewise, SerpinB1, a protease inhibitor which is upregulated in hepatocytes of insulin-resistant mice (e.g. LIRKO) via a FoxO1-dependent mechanism, stimulates β-cell proliferation in both murine and human islets. In fact, SerpinB1 serum levels directly correlate with insulin resistance in non-diabetic subjects, and loss-of-function variants are associated with multigenerational diabetes in humans. Conversely, inhibition of SerpinB13 results in enhanced β-cell development and could also have effects on adult human β-cell expansion.

While the use of murine models has aided in the identification of a plethora of agents able to boost β-cell duplication (including glucose, insulin, IGF-1, incretins and their analogues, placental hormones, platelet-derived growth factor, leptin, serotonin, growth hormone, and parathyroid hormone-related protein), many of them have failed to act as β-cell mitogens in human samples. Such discrepancies are partially attributable to the structural and biological differences between rodent and human islets. Indeed, the composition and expression levels of cell cycle proteins are different between β-cells from both species. For example, the of Cyclin D3 and CDK6 is critical for the onset of the cell cycle in humans but not in mice, expression whereas Cyclin D2 is expressed in mouse β-cells yet is virtually absent in their human counterparts. In this context, worldwide initiatives such as the NIH's Human Islet Research Network (HIRN) or the Network for Pancreatic Donors with Diabetes (nPOD) mark a progressively diminished reliance on murine models and hail a renewed and square focus on the human pancreas. Among these human-centric models, islets still represent the gold standard to study β-cell proliferation.

The preservation of the 3D structure maintains the *in vivo* organization, including cell-ECM and cell-to-cell interactions, allowing for a better translation to *in vivo* studies. However, the variability inherent to the donors and isolation methods, as well as their shipment from islet procurement centers, present challenges that often affect the reproducibility of the data from lab to lab. Human β-cell lines circumvent this problem and can be readily used, cultured as monolayers, to study transcriptomic and proteomic changes following treatments with mitogens, or to investigate the causes of β-cell death in T1D and T2D. In particular, the EndoC-βH3 cell line mirrors the basal proliferation rate of primary human β-cells, following drug-mediated excision of the immortalizing genes. This feature allows proof-of-concept experiments to proceed before validation in human islets. Furthermore, they can be transfected for silencing or overexpressing candidate genes involved in β-cell regeneration and therefore employed in large-scale studies for compound or CRISPR/Cas-9 library screenings. As described in earlier sections, advances in stem cell differentiation have enabled the generation of sBCs with islet-like properties.

These endocrine cells further aggregate into 3D islet organoids or “pseudoislets” that can be employed in studies aimed at the identification of agents and molecular signaling pathways regulating β-cell growth and survival. The relatively short time needed to generate these cells can compensate for the restricted availability of primary human islets, especially as sBC generation is progressively becoming mainstream. Finally, human pancreatic slice (HPS)-based technologies have recently stormed the field as a powerful model that preserves the integrity of the human pancreas, including native endocrine–exocrine interactions, for extended periods. This model affords the study of β-cell regeneration in an *in vitro* context that is even truer to nature than isolated islets, the standard bearer up to this point.

Chapter 5: Advances in Diabetes Research

Research in diabetes is constantly evolving, leading to new insights into the causes, prevention, and treatment of the disease. Advances in genetics, immunology, and technology are paving the way for more effective diabetes management and potential cures.

Genetic Research

Genetic research has provided valuable insights into the underlying causes of diabetes and potential targets for treatment.

Types 1 and 2 diabetes appear to be caused by an interplay of genetic, environmental, and lifestyle factors.[1] Over the years, researchers have found an array of specific genes that are linked to diabetes risk.

The genes that have been identified have diverse functions and duties which can affect blood sugar (glucose) control. Such functions include controlling the release of insulin, pumping glucose into cells, and speeding up the breakdown of glucose.

But, in addition to genes, something in the environment must trigger diabetes to become active. Researchers have found a number of factors that could trigger type 1 diabetes in people who are predisposed to it, including:[1]

- Exposure to some viruses
- Living in a cold climate
- Being introduced to solid foods at an earlier age
- Not being breastfed

Type 1 Diabetes

People genetically predisposed to type 1 diabetes have a higher chance of developing it, but that does not mean they absolutely will.

The risk of developing diabetes varies depending on a person's relationship to a family member with the condition. For instance:[4]

- Women with type 1 diabetes have a 1.3% to 4% chance of passing it on to their child
- Men with type 1 diabetes have a 6% to 9% chance of passing it on
- A non-identical sibling of someone diagnosed with type 1 diabetes has a 6% to 7% chance of developing the disease
- An identical twin of someone with type 1 diabetes has a more than 70% chance

In addition, type 1 diabetes is most common among non-Hispanic whites, especially those of Northern European descent.[4] This is connected to genes called HLA-DR3 or HLA-DR4, which are linked to autoimmune disease.

Suspect genes in other ethnic groups may put people at increased risk. For example, scientists believe that the HLA-DR7 gene may put Black people at risk, and the HLA-DR9 gene may put Japanese people at risk.[1]

Genetic predisposition alone is not enough to cause type 1 diabetes. And some people can develop type 1 diabetes even though no one in their family has it. It is estimated that 85% of the people diagnosed with type 1 diabetes do not have a family history of the disease.[5]

Type 2 Diabetes

Type 2 diabetes is characterized by insulin resistance and the progressive loss of cells in the pancreas that are responsible for making insulin (beta cells). As a result, blood sugar levels go uncontrolled. This is the most common form of diabetes.[6]

Many people who have type 2 diabetes may also have other underlying health conditions, such as high blood pressure, cholesterol, and excess weight in the abdominal area. In the past, type 2 diabetes was often referred to as adult diabetes, but it is now known that children can be affected too.

The genetic component of type 2 diabetes is complex and continues to evolve. Many genes have been identified in people with type 2 diabetes.

Some genes are related to insulin resistance, while others are related to beta cell function. Scientists continue to research genes involved in the development of type 2 diabetes and their role in disease progression and treatment.

Studies have shown a wide range of statistics for the heritability of type 2 diabetes—anywhere from 20% to 80% are thought to inherit it.[7]

The lifetime risk of developing type 2 diabetes is 40% for individuals who have one parent with type 2 diabetes, and 70% if both parents are affected. People who have a first-degree relative with type 2 diabetes are estimated to be three times more likely to develop the disease.[7]

But genetic factors are not the only risk. While type 2 diabetes has a stronger link to family history than type 1 diabetes, environmental and behavioral factors also play a role. As such, interventions can help to prevent or delay a diabetes diagnosis.

Gestational Diabetes

Gestational diabetes occurs during pregnancy when blood glucose levels become elevated. The placenta provides the baby with nutrients to grow and thrive. It also produces a variety of hormones during pregnancy.

Some of these hormones block the effect of insulin and can make after-meal blood sugars harder to control. This "contra-insulin effect" usually happens around 20 to 24 weeks of pregnancy, which is why people are screened for gestational diabetes at this time.

The US Preventive Services Task Force advises screening for diabetes in women who:

- Are planning a pregnancy, especially if they have type 2 diabetes risk factors
- Are pregnant and have diabetes risk factors—healthcare providers should consider screening them before 24 weeks of pregnancy
- Are pregnant and were not screened before conception—they should be screened at their first prenatal visit

Normally, the pancreas will produce more insulin to make up for hormonal insulin resistance. For some people, their pancreas cannot keep up with insulin production, which results in elevated blood sugar and a gestational diabetes diagnosis. Most women who develop gestational diabetes will have no symptoms.

Several genes have been identified in people with gestational diabetes. Studies suggest there may be a link between genes for gestational diabetes and type 2 diabetes.

Many people diagnosed with gestational diabetes have a close family member such as a parent or sibling with the disease or another form of diabetes, such as type 2 diabetes. Gestational diabetes appears to run in families.

Like other forms of diabetes, having a genetic predisposition doesn't mean you are guaranteed to get gestational diabetes. Other risk factors include gestational age, weight, activity level, diet, previous pregnancies, and smoking, to name a few. Maintaining adequate blood sugar control is important for the health of the mother and baby.

Genetic Testing

Genetic testing can be used to identify certain forms of diabetes that are monogenic, meaning that they are related to a change or defect in a single gene. Both neonatal diabetes and MODY are monogenic, and both tend to be incorrectly diagnosed.

Genetic testing is important for making a precise diagnosis, particularly for these monogenic types of diabetes. Furthermore, without a correct diagnosis, the affected person cannot get the proper treatment for the type of diabetes they have.

Physicians often recommend genetic testing when a diabetes diagnosis appears to be atypical. For example, a person who is around age 20 to 25, has abnormal blood sugars, and who does not have any typical risk factors for type 1 or type 2 diabetes, may have MODY.

Genetic diagnosis of MODY additionally allows for the identification of at-risk first-degree family members, who have a 50% chance of inheriting a gene mutation.

Unfortunately, insurance often denies coverage for genetic testing even when people fit the criteria, which can cause physicians to miss a MODY diagnosis. Researchers are continually trying to find ways to make genetic testing more cost-effective.

People found to be in the early stages of developing type 1 diabetes may also be eligible for the prevention study. Ask your healthcare provider whether genetic testing is available and how helpful it is in determining if you will get diabetes.

Whereas MODY and neonatal diabetes are monogenic, diabetes type 1 and type 2 are polygenic, meaning they are related to changes in multiple genes.

Currently, researchers do not feel that genetic testing is ready to diagnose type 2 diabetes. Because there are so many variants of genes and subtypes of type 2 diabetes, they feel as though better methods and more research need to be done in this area before putting it to practical use.

Similarly, genetic testing is not yet clinically useful for diagnosing polygenic gestational diabetes, as researchers have yet to identify a clear pattern of inheritance.

- **Monogenic Diabetes:** Research into monogenic forms of diabetes, such as MODY, has revealed specific genetic mutations responsible for the disease. These findings have led to more accurate diagnosis and personalized treatment options.

- Monogenic diabetes refers to a single gene defect that results in diabetes and is usually inherited in an autosomal dominant or recessive fashion. Monogenic diabetes can be broadly subclassified into neonatal diabetes, presenting before 6 months of age, and maturity onset diabetes of the young (MODY), presenting in youth and adults. Mutations causing diabetes may also be encountered in mitochondrial DNA and these are maternally inherited.

- Estimates of MODY prevalence vary depending on the population studied and how they were stratified for testing. Whilst neonatal diabetes is rare, affecting approximately 1 in 100,000 births, MODY accounts for between ~ 1 and 4% of all cases of diabetes in those diagnosed under the age of 30 years.

- The majority of MODY cases are accounted for by mutations in one of four genes: the transcription factors, hepatocyte nuclear factor 1-alpha (*HNF1A*), 4-alpha (*HNF4A*), 1-beta (*HNF1B*) and the enzyme, glucokinase (*GCK*) . Since the discovery of these initial four genes as causes of MODY, rare mutations in other genes have also been identified, expanding the spectrum of genetic aetiologias in diabetes. In neonatal diabetes, the most commonly affected genes are *KCNJ11* and *ABCC8*, encoding the two subunits of the ATP-sensitive potassium channel of the beta cell .

Table 1

Genes implicated in monogenic diabetes; MODY and neonatal diabetes

Gene	Protein	Function	Inheritance
Maturity onset diabetes of the young			
Common causes of MODY with well-established evidence-base			
HNF1A	Hepatocyte nuclear factor 1α	Beta-cell transcription factor	Autosomal dominant
HNF4A	Hepatocyte nuclear factor 4α	Beta-cell transcription factor	Autosomal dominant
GCK	Glucokinase	Glucose-sensor, first rate-limiting enzyme in glycolysis	Autosomal dominant

HNF1B	Hepatocyte nuclear factor 1β	Beta-cell transcription factor	Autosomal dominant
ABCC8	Sulphonylurea receptor subunit of β-cell K-ATP channel	Closure of the ATP-sensitive potassium channel leads to beta-cell membrane depolarisation, calcium influx and fusion of insulin secretory granules with beta-cell membrane	Autosomal dominant
KCNJ11	Potassium channel subunit of β-cell K-ATP channel		Autosomal dominant
INS	Insulin	Production of insulin or insulin action	Autosomal dominant
Rare causes of MODY with reasonable evidence supporting			
NEUROD1	Neurogenic differentiation factor 1	Beta-cell transcription factor	Autosomal dominant
IPF1	Insulin promotor factor 1	Beta-cell transcription factor	Recessive
CEL	Carboxyl ester lipase	Exocrine pancreas function	Deletion of variable number tandem repeat
WSF1	Wolframin	Function of the endoplasmic reticulum	Recessive
RFX6	Regulatory factor X 6	Beta-cell transcription factor	Dominant protein truncating variant
APPL1	Adaptor protein, phosphotyrosine interaction, PH domain, and leucine zipper containing 1	Protein that bind to AKT in the insulin-signalling pathway	Autosomal dominant

Neonatal diabetes

Causes of neonatal diabetes, accounting for > 2.5% of cases

ABCC8	Sulphonylurea receptor subunit of β-cell K-ATP channel	Closure of the ATP-sensitive potassium channel leads to beta-cell membrane depolarisation, calcium influx and fusion of insulin secretory granules with beta-cell membrane	Dominant, often de novo or recessive
KCNJ11	Potassium channel subunit of β-cell K-ATP channel		Dominant, often de novo
GCK	Glucokinase	Glucose-sensor, first rate-limiting enzyme in glycolysis	Autosomal recessive
GATA6	GATA binding factor 6	Transcription factor	Dominant, often de novo
INS	Insulin	Production of insulin or insulin action	Dominant, often de novo or recessive
PTF1A	Pancreatic associate transcription factor 1 A	Transcription factor involved in pancreatic development	Recessive
EIF2AK3	Eukaryotic translation initiation factor 2 alpha kinase 3	Kinase enzyme in endoplasmic reticulum	Recessive
RFX6	Regulatory factor X 6	Beta-cell transcription factor	Recessive

Some of the information in Table Table11 came from https://www.diabetesgenes.org/tests-for-diabetes-subtypes/targeted-next-generation-sequencing-analysis-of-45-monogenic-diabetes-genes/" [5]

Making a diagnosis of monogenic diabetes has several benefits, which include: targeted treatment depending on the affected gene that is often superior to conventional approaches ; family member cascade testing to identify other, often misdiagnosed cases and prediction or early identification of other multisystem features that may be associated with the genetic defect.

Though the clinical benefits of a diagnosis are increasingly clear, significant challenges still remain. The first of these is to improve the identification of misdiagnosed cases as evidence suggests many are still misclassified. In particular, a shift in focus towards the identification of MODY across all ethnic groups is warranted, as in certain ethnicities the overlapping features of young-onset type 2 diabetes and MODY are likely to obscure detection. Closely related to this is the need to improve accessibility of sequencing technologies and develop a standardized approach to select or stratify appropriate individuals for genetic testing, with consensus criteria that have transethnic applicability. Perhaps most importantly, though, is the need to ensure quality interpretation of genetic sequencing data that is clinically translatable and meaningful along with the need for consistency in classifying a gene as potentially causing monogenic diabetes.

The biggest barrier to making a diagnosis of monogenic diabetes is lack of clinical suspicion or awareness. A UK study in 2012 demonstrated a marked geographical variation in referral to a centralized genetic testing laboratory. Raising awareness of genetic forms of diabetes and recognizing atypical features in people diagnosed with type 1 or type 2 diabetes, is therefore key. Though the cost of genetic testing continues to fall, it is still relatively expensive, and testing is recommended in those individuals with a moderate to high possibility of a positive finding. Worldwide access to quality genetic testing services remains problematic.

Clinical Approach

The original clinical criteria to define MODY included an age of onset below 25 years, not requiring insulin treatment and having a generational family history of diabetes. Since this first description, however, the criteria have proven to be insensitive in many confirmed cases, as well as increasingly non-specific.

This is unsurprising with the rising prevalence of young-onset type 2 diabetes that is, at diagnosis, non-insulin requiring like MODY and typically occurs in the setting of a strong family history. Indeed, in some cases of adult-onset type 1 diabetes, the slow progression to beta-cell failure may not require insulin treatment immediately; thus, the lack of a need for insulin is not particularly discriminatory for monogenic diabetes. Additionally, a family history of diabetes is often encountered in many people with any type of diabetes, again, due to the rising prevalence of type 2 diabetes. In addition, it is recognized that > 20% of children with confirmed type 1 diabetes have an affected first-degree relative after decades of follow-up. Age at onset below 25 years is also an arbitrary cut-off and, although commoner in younger adults, confirmed MODY mutations can present into the 5th decade of life.

In ethnic groups with a higher prevalence of young-onset type 2 diabetes, the discriminatory value of these criteria is even poorer. Indeed, in one study of UK south Asian individuals referred for genetic testing, although the south Asian referrals were more likely to meet the clinical referral criteria than white individuals, the detection rate of MODY in those genetically tested was less than half of the white group

The MODY probability calculator offers a more standardized approach to select individuals for genetic testing. The online calculator combines broad clinical information to predict the probability of testing positive for MODY. When compared to traditional criteria, the prediction model improved the sensitivity and specificity for identifying MODY. However, the model was developed and validated in the same cohort of white individuals of European descent. There is a need for validation in other cohorts and some early studies in east Asians have shown good sensitivity but reduced specificity.

Biomarker Approach

With non-specific clinical criteria, attention has turned to the use of biomarkers that assist the selection of individuals for genetic testing. C-peptide, pancreatic autoantibodies, lipid profiles and high-sensitivity C-reactive protein (CRP) have variable discriminatory value, but also have several limitations. Pancreatic autoantibodies are positive close to diagnosis in ~ 80% of people with type 1 diabetes if glutamic acid decarboxylase (GAD) and insulinoma antigen-2 (IA2) antibodies are measured, although titers may decrease with duration of diabetes, and a negative result does not therefore exclude type 1 diabetes. People from some ethnic groups with type 1 diabetes have been shown not to have detectable autoantibodies at diagnosis, and so again the absence of pancreatic auto-antibody positivity does not preclude a diagnosis of type 1 diabetes.

C-peptide levels, a marker of endogenous insulin production, have also been used to help segregate people with type 1 diabetes (where C-peptide is low or undetectable) from those with MODY. However, this is not useful at diagnosis of diabetes, where C-peptide may be detectable in early type 1 diabetes, and even in long duration type 1 diabetes approximately 8% of people have stimulated C-peptide levels well above thresholds considered typical for type 1 diabetes. Similarly, individuals with severe hyperglycemia due to either monogenic or type 2 diabetes may have undetectable C-peptide levels due to transient beta-cell glucotoxicity.

Practically, a combination of clinical and biomarker approaches is likely to yield the highest sensitivity. In the US SEARCH study, youths diagnosed with diabetes below the age of 30 years were selected for genetic testing if pancreatic auto-antibody testing was negative and fasting C-peptide >0.8 ng/ml and yielded a detection rate of 8% in those tested. In the Young Diabetes in Oxford study, a pick-up rate for MODY of 15% was observed in those with type 2 diabetes diagnosed before 45 years without features of insulin resistance or 10% of those with type 1 diabetes from individuals selected on the basis of antibody negativity and preserved C-peptide. The UK UNITED study demonstrated a MODY prevalence of 3.6% using a biomarker approach in those diagnosed < 30 years with diabetes, a detectable urine C-peptide and negative antibodies. In this study, the MODY probability calculator also missed 55% of cases identified using the biomarker approach. Recently, the Norwegian childhood diabetes registry was used to estimate MODY prevalence in all the antibody-negative children in the registry, which has a high case ascertainment. A total of 4.1% of individuals had likely pathogenic or pathogenic variants in the commonest MODY genes (*HNF1A*, *HNF4A*, *HNF1B*, *GCK* or *INS*). The biomarker approach is likely to result in more individuals being selected for testing. However, since the cases identified in those tested appear to be less likely to meet clinical criteria or are missed by the MODY probability calculator, testing more individuals may be warranted.

Genetic Risk Scores

When antibodies are negative and C-peptide levels are preserved, the clinical picture could be consistent with type 1, type 2 or monogenic diabetes. In these cases, assessing probability of type 1 or type 2 diabetes on the basis of polygenic risk, so-called genetic risk scores, may have some additional discriminatory value. A genetic risk score for type 1 diabetes that incorporates key human leukocyte antigen (HLA) susceptibility loci has been shown to facilitate discrimination of type 1 from monogenic diabetes and type 2 diabetes. However, as with other approaches, this was validated in white European populations and evidence suggests ethnic-specific variations will be required.

In practice, misclassification of all diabetes types may occur, and healthcare practitioners need be alert to this possibility. The application of a systematic approach to individuals who are newly diagnosed, particularly young adults and in those from non-white ethnic groups, could assist classification of common forms of diabetes and identify those in whom molecular investigation would be beneficial. Using biomarkers in this strategy is worthwhile if the limitations of these specialist tests are appreciated.

Identifying Monogenic Diabetes Across Ethnic Groups

To date, monogenic diabetes has predominantly been studied in populations of European descent and systematic studies in other ethnic groups are lacking. In the UK, MODY was first reported in the south Asian ethnic group in a systematic survey of childhood diabetes. A 2006 study revealed a lower-than-expected frequency of referrals for MODY testing in the south Asian ethnic group. However, it was unclear if this reflected a genuinely lower MODY prevalence in this group or under-diagnosis due to referral bias and numbers were too small to explore the clinical characteristics of patients.

In a follow-up UK study from 2016, confirmed MODY mutations were observed in a variety of UK ethnic groups, including south Asian and African-Caribbean, though the detection rate was lower in these groups, compared to white. Interestingly, south Asian people referred for testing were more likely to meet clinical referral criteria.

The SEARCH study identified MODY mutations in African American and Pacific Islander youths. *HNF1A*, *HNF4A* and *GCK* mutations had been detected in various reported studies from India, although the assessment of what constitutes a pathogenic mutation versus a benign nucleotide change remains challenging. Monogenic diabetes has also been detected in many east Asian populations, including China and Japan.

Lessons can be learnt from a study of comprehensive testing for neonatal diabetes in 79 countries, which demonstrated variability in mutation frequency and inheritance patterns depending on the population studied . For example, recessive *E1F2AK3* mutations were most common in countries with higher prevalence of consanguineous unions whereas mutations in *KCNJ11* and *ABCC8* predominate elsewhere. A recent study in Oman demonstrates a higher frequency of recessive *GCK* mutations.

It is likely that the lower reported number of cases of MODY in non-white ethnic groups reflects a more challenging clinical separation from those with young-onset type 2 diabetes. For example, type 2 diabetes in south Asians is associated with a leaner body mass index (BMI) and stronger family history, and proportions of antibody positive individuals in non-white ethnicities with type 1 diabetes appear to be lower in native countries, although systematic assessment is lacking.

In preliminary data from the MY DIABETES study, the biomarker approach found similar detection rates of MODY across UK south Asian, African-Caribbean and white ethnic groups. As the number of cases of young-onset type 2 diabetes continues to rise, and because obesity can co-present with any form of diabetes, including MODY, clinicians may have to expect to test more individuals to identify hidden cases of MODY, especially in ethnic groups with a high prevalence of younger-onset type 2 diabetes.

Testing Individual Genes Versus a Panel

The facility to sequence known MODY-causing genes using targeted next-generation sequencing technologies has enabled the rapid recognition of mutations in people presenting with a MODY phenotype. Molecular genetic testing has traditionally been guided by the clinical phenotype and also the relative prevalence of mutations within any given population. In people with a very specific clinical phenotype, it might be pragmatic to request Sanger sequencing (a method that sequences a single gene in a single reaction) of the selected gene alone; for example, *GCK* testing in a patient with isolated fasting hyperglycemia, or *HNF1B* testing in a patient with renal cysts and diabetes.

In other types of monogenic diabetes, however, it may be difficult to predict the affected gene on the basis of clinical features alone. Previously, this situation would result in sequential testing of multiple genes, using Sanger sequencing. This could often result in long delays before a diagnosis was obtained. However, advances in DNA sequencing technologies have meant that now panels of genes can be tested simultaneously using next-generation sequencing platforms without the considerable costs and time associated with earlier sequencing approaches [1,45]. This approach mitigates somewhat against the circular paradigm of defining specific phenotype in individuals with associated genotypes, but only testing those individuals with the phenotype in the first place. Thus, it may be the case that individuals with the same mutation could present differently, but because only those with the 'defined' phenotype are being tested, those other individuals are not detected.

Studies using targeted next-generation sequencing (tNGS) approaches have found mutations in genes other than the common MODY genes. For example, in the UNITED study, 74% of known MODY cases had mutations in *HNF1A*, *HNF4A* or *GCK*. However, using a biomarker approach with tNGS, 47% had mutation in these genes .

The availability of robust panels of diabetes genes that incorporate coding and potentially regulatory regions will be laboratory-dependent and is not widely agreed or available. However, limiting testing to the common MODY genes clearly misses cases of MODY in other genes that may have real impact on management, for example MODY mutations in *ABCC8* or mitochondrial diabetes, testing for which has been incorporated into some panels.

Is the Variant Pathogenic?

Determining pathogenicity of a variant is now the biggest challenge in the interpretation of exome-based sequencing data and of huge importance in the clinical context, where incorrect interpretation can have serious clinical consequences. Assigning pathogenicity is a particular issue in genes associated with monogenic diseases such as MODY, where distinguishing between variants that are clearly disease-causing versus those that impair protein function or are neutral, is problematic.

This issue is further complicated by the fact that many of the variants found in the common MODY genes are novel or arise de novo, making it impossible to gain insights from other affected individuals.

A variety of guidelines, both national and international, have attempted to standardise the approach to investigating variant pathogenicity using in silico modelling, database searches and other parameters to assist with classification and to also standardise notation . Variants are graded from 1 to 5; 1, benign; 2, likely benign; 3, variant of unknown significance; 4, likely pathogenic; and 5, pathogenic; and guidelines stipulate that variants classed between 3 and 5, should be reported to requestors.

Table 2

Strategies to establish pathogenicity of a variant in diabetes genes

Approach	Parameter	Description
In silico data	Genome database searches	Search of genome/exome databases e.g. GnomAD to establish mean allele frequency and also assess presence of other variants at affected nucleotide position
	Sequence variant databases	For example, dbSNP, Exome Variant Server or 1000 genomes NGRL
	Mutation database searches	Human Mutation Genetic Database search, imports published data on genetic mutations. Limitations, as mutations published may not necessarily prove to be pathogenic
	Amino acid change	Examines the effect of the amino acid substitution on charge and polarity. A significant change in polarity or charge from the amino acid substitution might be more likely to impair protein function
	Species conservation	Conservation can be scored using tools such as ConSurf, through which multiple sequence alignments can be undertaken to compare orthologs across species. Essential sites for protein function are likely to be invariant across species (highly conserved)

	Software prediction	Software prediction models: SIFT, PolyPhen2 and AlignGVGD Grantham Distance assessed the physico-chemical difference

One such database is the Genome Aggregation Database (GnomAD), which contains data from over 100,000 exomes and 15,000 whole-genomes. GnomAD reports minor allele frequency (MAF) depending on ancestry. These databases can be used to assess whether a variant found in a dominant gene might be disease-causing.

For example, the presence of a variant in more individuals than would be predicted from the population prevalence of MODY (50–100 per million [9]), assuming complete penetrance, would indicate that the variant is not acting as an autosomal dominant pathogenic mutation, since it would be present in people without disease.

However, knowledge of MAF is not a magic bullet. Each exome in GnomAD contains an average of 7.6 rare variants (MAF < 0.1%) in Mendelian disease genes, which suggests tolerance to genetic variation is higher than previously assumed. Such data have been used to downgrade pathogenicity status in variants that have previously been thought to be disease-causing.

The spectrum of low-frequency variation (MAF < 1%) in the seven commonest genes associated with MODY was examined in 4003 individuals from population studies. Although 1.5% of those studied harbored genetic variants that had been previously reported to cause MODY, the majority were still euglycemic through to middle age. This study was an early indication that careful consideration in assigning pathogenicity to variants in dominant genes, is needed.

Species Conservation

Species conservation measures the degree to which amino acid properties at any given position are evolutionarily conserved. Essential sites for protein function are likely to be invariant across species (highly conserved), whereas a variant sites across species can, by definition, accommodate a degree of substitution. Therefore, missense variants encountered at highly conserved sites are more likely to be pathogenic.

In Silico Predictions

Using web-based applications, missense variants can be classified based on the predicted effects of the variant on protein function. The prediction obtained from a single method should not be taken in isolation. Broadly speaking, four main approaches exist: those based on sequence conservation methods; those assessing impact on protein sequences; protein structure; and physicochemical properties and splicing-predictions.

Software programs such as SIFT (J. Craig Venter Institute, La Jolla CA), Align-GVGD (International Agency for Research on Cancer hosted by the World Health Organization and PolyPhen-2 can combine a variety of assessments to predict pathogenicity.

Despite these aligned approaches, it is still often difficult to confidently assign pathogenicity. In these cases, further work may be necessary to shed light on variant functionality. These may be clinical studies in the individual or family members, or by use of reliable in vitro functional or biochemical assays that assess the effect of the variant in a cellular system model. Even then, confident assignment of pathogenicity may not always be possible due to the limitations of these techniques.

In Vitro Functional Studies

A series of assays have also been described to investigate transcription factor variants, such as those in *HNF1A,* based on published studies. For the *HNF1A* gene, which has been studied extensively, these include an assessment of transactivation potential (the transcriptional activity of HNF1A), protein production, nuclear-cytosolic localization and DNA-binding in cellular systems.

In vitro functional studies have also been successfully deployed in cases of neonatal diabetes to support precision-based treatment. In individuals with *KCNJ11* mutations causing neonatal diabetes, the success of sulphonyl urea treatment is determined by the specific mutation, as not all affected channels are sensitive to blockade. Knowledge of specific mutant effects in vitro can therefore help clinicians decipher whether to try higher doses to achieve full blockade of the channel, or whether insulin is needed.

Guidelines recommend collaboration with molecular laboratories in cases where functional effects of variants using established techniques prove inconclusive, but where there is real clinical impact in assigning status. However, this may be challenging for clinicians to access readily as most MODY gene variants have not been studied in this way and accessible pathways to support these efforts routinely may need to be developed.

In practice, for people with monogenic diabetes, treatments can be trialed empirically with or without confirmed mutation status, but the frustration and anxiety in failing to receive a conclusive diagnosis in those with variants of unknown significance is high and the psychological burden remains unexplored.

Clinical studies

In many cases, the clues towards pathogenicity come from studying the proband and their family members in more detail. For novel variants, familial co-segregation studies that demonstrate the variant in relatives with diabetes, but absence in those without diabetes, is compelling evidence in favor of pathogenicity. Similarly, demonstrating sulphonyl urea sensitivity in those with uncertain variants in *HNF1A* or *HNF4A* can also be very helpful.

Is the Gene or Variant Really Causing Diabetes?

Aside from the common MODY genes described, a number of other genes have been implicated as causing diabetes. These include the beta-cell transcription factors *IPF1* and *NEUROD1,* and *PAX4*, *KLF11* and *BLK.* The genetic evidence for these genes causing penetrant autosomal dominant monogenic diabetes is weak and initial findings have not been borne out from large-scale sequencing panels of genes.

Extremely rare mutations in other genes have also been identified. For example, deletions shortening variable number tandem repeats in the *CEL* gene appear to cause diabetes and pancreatic exocrine dysfunction and specific mutations in *POLD1* can result in severe insulin resistance syndromes. Loss of function variants in *APPL1* have also been identified in two families from an exome sequencing study. Co-segregation studies are promising, but it will remain to be seen whether *APPL1* variants will be reported in other MODY.

Understanding the phenotypic spectrum of variants from benign to disease-causing in dominant genes is also key. Common variants in *KCNJ11* and *GCK* can lead to small changes in glucose homeostasis, whilst less common variants leading to a more severe functional impact cause MODY and neonatal diabetes. Another example is the low-frequency E508K variant in *HNF1A*, which in the Latino population appears to increase risk of type 2 diabetes rather than causing monogenic diabetes.

A similar finding has been observed in the Wolfram syndrome gene *WFS1,* which causes a MODY-like phenotype in a small number of families, but common variation in the gene is also associated with risk of type 2 diabetes.

As new data are gathered, revisiting existing genes can also be helpful. Protein truncating variants in the beta-cell transcription factor *RFX6* have now been reported to cause MODY with low penetrance. Previously, however, only homozygous mutation in *RFX6* had been implicated in neonatal diabetes with gut and gallbladder anomalies and the role as a MODY-gene was questionable due to variable penetrance. Protein truncating variants robustly co-segregate with diabetes, but with an increased age of onset compared to HNF1A-MODY, as only 27% had developed diabetes by age 25, compared to 55% of HNF1A-MODY cases

Management of Monogenic Diabetes

The management of monogenic diabetes is based predominantly on observational data. The main application of personalized medicine is in the use of sulphonyl urea (SU) agents in *HNF1A/HNF4A*–MODY and in neonatal diabetes caused by mutations in K-ATP channel components. This is supported by a small randomized controlled trial of gliclazide versus metformin in *HNF1A*-MODY and in observational data collected in cases of neonatal diabetes. Therefore, people with mutations in *HNF1A* or *HNF4A* causing MODY can be managed with low-dose sulphonyl urea therapy, and those misdiagnosed may therefore potentially stop insulin injections or have tablet regimens rationalized.

These precision-based treatments not only achieve good glycemic control, but there is compelling evidence demonstrating that they are superior to conventional approaches. There are case reports of decades of successful treatment on SU therapy in *HNF1A*-MODY, although clinicians also, not infrequently, see cases who do not respond well despite possessing an *HNF1A* variant that is clearly diabetes-causing (personal observation). The reason for this variation in treatment response remains unclear. However, a recent study has suggested that higher HbA1c, higher BMI and longer duration of diabetes at the time of transfer to SU therapy from insulin, may predict failure of SU monotherapy, making the case for early genetic diagnosis.

A study of liraglutide use in *HNF1A*- and *GCK*-MODY examined both clinical response and mechanistic aspects. This study showed no significant difference in glucose lowering effect between liraglutide and SU treatment, but more hypoglycemia with SU use, suggesting that the SU dose used was too high. The additional expense and inconvenience of injection therapy does not appear to justify routine GLP1 therapy in *HNF1A*-MODY, and it is unknown how effective these agents would be in the context of long duration MODY with secondary SU failure. Most clinicians use metformin or a dipeptidyl peptidase-4 inhibitor as second-line treatment although there is no particular evidence base.

The effect of sodium-glucose transporter-2 inhibitor agents in HNF1A-MODY, who already have decreased expression of *SGLT2* and low renal threshold, was shown in a single dose study to induce greater glycosuria than in type 2 diabetes [80] and it is unknown whether this would lead to greater adverse effects or increased efficacy of the agents.

Permanent neonatal diabetes (PND) caused by mutations in *KCNJ11* or *ABCC8* can be managed with high dose sulphonyl urea therapy in > 90% of cases, negating the need for insulin therapy and associated complications in affected neonates. For neonatal diabetes, a recent case series of 10-year follow-up of individuals with *KCNJ11* or *ABCC8* variants treated with SU agents reported that 93% of cases remained on SU therapy alone, achieving glycemic targets and with a good safety profile.

GCK MODY, characterized by lifelong, non-progressive fasting hyperglycemia, requires no pharmacological therapy and, following diagnosis, affected individuals may be able to stop all treatment. In the largest longitudinal study to date of people with *GCK* mutations, there is no higher burden of clinically significant microvascular or macrovascular complications, compared to normoglycemic individuals.

Most other forms of MODY, neonatal diabetes and mitochondrial diabetes are characterized by insulin deficiency and therefore, in most cases, individuals progress to insulin therapy. Those with mitochondrial diabetes tend to have increased lactate levels, which has raised concerns over metformin use, although there is no evidence that there is an increased prevalence of lactic acidosis, since metformin only appears to cause lactic acidosis in the setting of severe renal dysfunction. The pragmatic consensus is that other oral agents should be used in preference to metformin, particularly in those with neurological features.

Further Research

The drive to deliver precision-based approaches in diabetes undoubtedly underpins many of the recent advances in monogenic diabetes, although there is still much to achieve. A critical step, as discussed, is to develop and validate strategies for finding cases of monogenic diabetes that have transethnic applicability.

Supporting clinical practitioners to understand and deliver often complex genetic information to people with diabetes is also a key area that lacks firm guidance. As accessibility to sequencing technologies expands, particularly in understudied populations, there is a potential harm from poor interpretation of variant pathogenicity that needs to be addressed. Close collaboration between clinical practitioners and centralized laboratories that undertake these activities may be helpful in this context.

Moving beyond monogenic diabetes and understanding the impact of common variants on type 2 diabetes risk, phenotype and treatment effects, is likely to be the next clinically meaningful direction for the lessons learnt from monogenic diabetes. Efforts to address this unmet need are underway and are very likely to change the approaches to management of common diabetes types.

There have been many advances in the field of monogenic diabetes, although considerable challenges remain. Improving awareness of monogenic diabetes and accessibility of cost-effective and high-quality genetic testing services remains a key challenge. Whilst stratified biomarker approaches to case-finding appear to be more successful than conventional clinical criteria, widespread applicability is limited due to the paucity of transethnic data. Much remains to be done to facilitate diagnostic pathways that are clinically safe, at a national level.

A crucial step underpinning such efforts will be the validation of existing strategies across multiple ethnic groups, and potentially development of new strategies where current practices proves to be ineffective. The rising incidence of young-onset type 2 diabetes continues to obscure the detection of monogenic diabetes, although meaningful approaches to segregate these cases are unlikely to be forthcoming and practitioners may have to expect to test more individuals if all monogenic cases are to be found.

Due to its significant socioeconomic impact on numerous nations, addressing diabetes mellitus (DM) requires continuous scientific and technological progress for the identification of innovative treatment approaches. Consequently, this has led to the emergence of novel therapeutic categories such as gastric inhibitory peptide (GIP) analogs, amylin analogs, and incretin mimetics. Furthermore, potential drug targets for diabetes treatment, specifically peroxisome proliferator-activated receptor (PPAR) and dipeptidyl peptidase-4 (DPP4) inhibitors, have been established.

Promoting the regeneration of β-cells by means of trans-differentiation or stem cell techniques has a direct impact on improving the function and structure of these cells. However, the field of gene therapy has recently emerged as a promising approach for managing diabetes, with numerous clinical studies demonstrating its safety and effectiveness in treating various complex diseases. Both viral and non-viral approaches to gene therapy have shown encouraging outcomes. For instance, gene therapy utilizing adeno-associated viral (AAV) vectors has been applied, and research indicates its potential for long-term regulation of blood glucose levels and prevention of diabetes-related complications.

To deliver the insulin gene to different tissues such as adipocytes, pancreas, livers, and muscles, viral methods such as lentivirus, adenovirus, and AAV have been used as well as non-viral techniques such as liposomes and naked DNA. Enteroendocrine K-cells in the intestines share similarities with pancreatic β-cells by producing GIP. Both cell types secrete GIP, which regulates insulin release in response to elevated blood glucose levels. Additionally, they possess comparable glucose-sensing mechanisms, shared transcription factors, and signaling pathways. This convergence highlights the interconnectedness of the gut and pancreatic endocrine systems in glucose regulation. Understanding these similarities can aid in managing metabolic disorders like type 2 diabetes. Further research may lead to innovative therapeutic strategies for improving glucose homeostasis.

The transplantation of K-cells has therefore failed to reverse diabetes effectively, despite attempts to manipulate them *in vitro* to produce and release insulin. After being induced with diabetes by streptozotocin (STZ), transgenic mice engineered to express insulin under the GIP promoter displayed normal glucose levels. This suggests that K-cells produce adequate amounts of insulin to maintain glucose homeostasis. Recently, gene manipulation techniques have been introduced for managing diabetes mellitus, utilizing adeno-associated viral (AAV) vectors to achieve the co-expression of insulin and glucokinase genes in skeletal muscles.

Notably, this approach has demonstrated long-term effectiveness in achieving normo-glycemia without the need for exogenous insulin. AAV vectors possess favorable characteristics for gene therapy, including minimal immune response, infectivity in both dividing and dormant cells, and absence of genome integration. AAV vectors are characterized by these attributes, which make them particularly suitable for gene therapy applications. Mice with diabetes induced by STZ were given AAV vectors that contained the insulin and glucokinase genes. When these two genes are co-expressed, glucose transporter protein 4 (GLUT4) and glucokinase enzymes are translocated to the modified muscle cells, increasing glucose absorption. As a result of the expression of the glucokinase enzyme, glucose phosphorylation was alleviated and insulin production was regulated, resulting in normo-glycemia.

Another approach to gene therapy for diabetes management involved the use of a humanized liver mouse model. Researchers utilized AAV serotype 2 (AAV2) to transfer the pancreatic and duodenal homeobox 1 (PDX1) gene, an enzyme that is involved in the development and maturation of pancreatic β-cells.

It was confirmed that green fluorescent protein was present and the liver cells containing the PDX1 gene secreted insulin, leading to glycemic control Adenovirus-mediated transfection of hepatic cells with neurogenin 3 (Ngn3) resulted in insulin production and trans-differentiation of oval cell populations. Introducing neuronal differentiation 1 (NeuroD1) into the liver of mice with STZ-induced diabetes upregulated various pancreatic transcription factors without causing significant liver damage. Furthermore, NeuroD1 had a strong effect on inducing insulin expression in primary pancreatic duct cells. Researchers suggested targeting promoters in specific cell types, such as liver-type pyruvate kinase (L-PK), glucose 6-phosphatase (G6Pase), phosphoenolpyruvate carboxykinase (PEPCK), albumin, and insulin-like growth factor binding protein-1 (IGFBP-1), to enhance hepatic insulin gene therapy. While liver-specific promoters showed insulin secretion, their activity was weaker compared to strong constitutive promoters like cytomegalovirus. Modifications using L-PK led to glucose responsiveness and restored normo-glycemia for a limited period

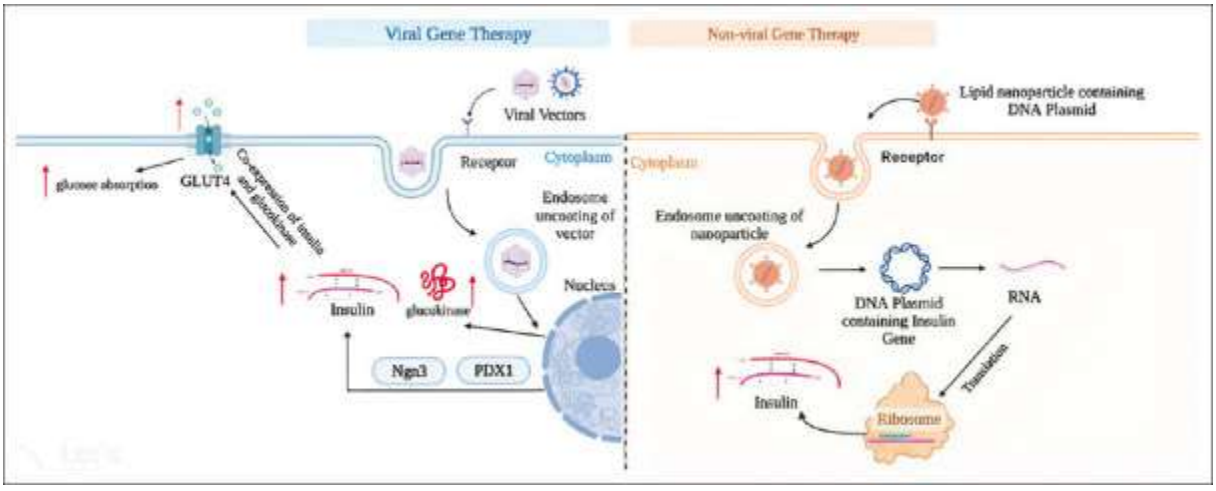


Figure 1

Gene therapy approaches for diabetes management: Viral and non-viral methods for insulin gene delivery to different tissues show promise in regulating glucose homeostasis. Adeno-associated viral (AAV) vectors co-expressing insulin and glucokinase genes in cells demonstrate long-term effectiveness in achieving normo-glycemia. GLUT4: glucose transporter protein 4, Ngn3: neurogenin 3, PDX1: pancreatic and duodenal homeobox 1

In the non-viral gene delivery method, insulin fragments were combined with plasmid DNA and administered via intravenous injection. This approach involved injecting plasmid into the liver and muscles of rats with STZ-induced diabetes. The result of the study is that normo-glycemia has been achieved in the subjects for one week and for thirty weeks, respectively. To address the issue of short-term liver expression, the DNA transposon system was employed, enabling the integration of the gene into the host chromosome. Furthermore, co-injecting plasmid DNA containing insulin with Furin significantly enhanced the production of active insulin within the muscle.

In a study, a non-viral plasmid, pBudCE4.1, was engineered to carry the genes for proinsulin (PI) and pancreatic regenerating (Reg) III protein. Findings were revealed that the introduction of pReg/PI effectively ameliorated streptozotocin-induced type 1 diabetes mellitus (T1DM) by promoting the regeneration of beta cells and inducing immunological self-tolerance. Additionally, the use of pVAX plasmid has been explored as another plasmid vector for gene transfer.

This non-viral approach allows transient expression of target genes in both liver parenchymal and non-parenchymal cells. In a specific study, researchers successfully expressed the insulin-like growth factor 1 (IGF-1) gene using the pVAX plasmid.

Notably, after receiving ten administrations, mice with normal blood glucose levels achieved prolonged therapeutic effects and did not require further treatment. Another study utilized a bioreducible cationic polymer called poly-(cystamine bisacrylamide-diamino hexane) (p(CBA-DAH)) to deliver RAE-1 to pancreatic islets in their study. The treatment group receiving polyplexes containing RAE-1 demonstrated an improvement in insulitis levels.

In addition, pancreatic or liver cells were transfected with the human insulin gene *ex vivo* and then autologous grafts were performed. Over the course of 47 weeks, this method was shown to improve insulin secretion, hyperglycemia, and diabetic complications in pigs. However, gene silencing eventually occurred, though the underlying mechanism remains unclear. Lentivirus vectors carrying the modified human insulin gene were also injected into the portal system of the livers of diabetic rats, enabling liver cells to sense glucose and respond by synthesizing, releasing, and storing human insulin

Treating diabetes by specifically targeting and regenerating β-cells

Trans-differentiation

Drugs currently used for diabetic treatment primarily focus on enhancing the sensitivity of β-cells to produce insulin to lower blood glucose levels. However, these medications often come with unwanted side effects, prompting research into alternative treatment approaches. Bonner-Weir *et al*. demonstrated that in cases of β-cell depletion in diabetes, the increased proliferation of remaining β-cells contributes to β-cell regeneration. In light of these findings, further investigation has been conducted into the neogenesis of insulin-producing cells from other types of cells, as observed in various injury models. Recent studies have focused on inducing β-cell regeneration through the trans-differentiation of different cell types. Researchers believe in the potential of pancreatic progenitor cells in the pancreas to undergo trans-differentiation and regenerate into β-cells. Among the relevant cell types for β-cell regeneration, pancreatic exocrine cells such as acinar cells and ductal epithelial cells have gained attention due to their pancreatic lineage and differentiation potential. It has been hypothesized that β-cell neogenesis from pancreatic progenitor cells can occur within the pancreatic ducts after birth. Some studies have provided evidence of β-cell generation from ductal tissue in the adult pancreas, particularly in response to injury-induced β-cell depletion resulting from duct ligation. However, recent studies utilizing labeling experiments of the ductal lineage have failed to conclusively demonstrate the formation of β-cells derived from ductal cells.

It is important to note that the clinical application of these findings is limited by factors such as organ shortage for transplantation and the need for immune-suppressant drugs, which have primarily been studied in animal models rather than in a human microenvironment. In addition to pancreatic progenitor cells, researchers have explored the potential of α-cells to convert into β-cells. Studies conducted using zebrafish models and β-cell ablation have shown promising results, but further research is required.

Stem cells

Stem cells have been investigated as alternative sources for β-cells due to limitations in the trans-differentiation of pancreatic progenitor cells. One alternative is the use of embryonic stem cells (ESCs) obtained from human embryos. However, ethical concerns arise due to their embryonic origin. Using somatic cell nucleus reprogramming, induced pluripotent stem cells (iPSCs) have been generated to overcome this limitation. iPSCs share comparable characteristics with ESCs and can be generated using small molecules and RNA. They offer the advantage of patient-specific cell replacement therapy. A lack of pancreatic differentiation in ESCs and iPSCs may be addressed by pancreatic progenitor cells (PPCs).

Mesenchymal stem cells (MSCs) have shown promise in diabetic therapy due to their immunomodulatory effects. They create a microenvironment that promotes β-cell regeneration while suppressing destructive T-Helper1 (Th1) cells. However, it is preferable to use MSCs therapy in combination with other treatment approaches. Undifferentiated MSCs do not directly generate new β-cells for regeneration. The media obtained from MSC culture has demonstrated therapeutic effects when injected into diabetic mice. This approach avoids issues of autoimmunity and oncogenesis, as it is cell-free in nature.

Bone marrow stem cells (BMSCs) have been utilized to replace damaged β-cells but produce low levels of insulin. Adipose tissue-derived stem cells (ADSCs) offer advantages such as low immunogenicity, higher immunomodulatory properties, and a higher capacity for stem cell proliferation compared to BMSCs. ADSCs can differentiate into insulin-producing cells (IPCs) and, when transplanted into the pancreas of STZ rats, have shown induction of pancreatic regeneration. In diabetic rats, the transplantation of differentiated IPCs improved the morphology and function of islet cells. ADSCs have also shown benefits in islet angiogenesis enhancement, reduced cell apoptosis, and improved insulin sensitivity.

The ability of human placenta-derived MSCs (PD-MSCs) to produce insulin has attracted attention. After intravenous injection of PD-MSCs, glycosylated hemoglobin levels were significantly decreased, and insulin and C-peptide levels were significantly increased in type 2 diabetes mellitus T2DM patients. As far as cardiac and renal function is concerned, no side effects, immune rejection, or changes have been observed.

Efforts to enhance the efficiency of generating functional stem cell (SC) β-cells necessitate a comprehensive understanding of the extracellular signals governing cell fate determinations during embryonic and postnatal development. However, the complete comprehension of the cues required to fully control the differentiation of embryonic stem cells (ESCs) into all islet endocrine cell types remains elusive. Presently, SC islet clusters typically contain a significant proportion of undesired non-pancreatic endocrine cells and progenitor cells that fail to undergo terminal differentiation, resulting in a limited number of desired endocrine cells.

To address this, methods such as fluorescence-activated cell sorting (FACS) and magnetic bead sorting are employed to enrich β- and α-cells and minimize the presence of undesired cells within SC islet clusters. Nonetheless, these sorting methods are accompanied by substantial cell loss, significantly reducing the overall efficiency of β-like cell production.

The optimal mimicry of human islet function necessitates precise regulation of the β to non-β endocrine cell ratio within the clusters. Existing differentiation protocols primarily prioritize the generation of β-like cells, leading to fewer α- and δ-like cells. The extent to which a pure population of β-like cells or the presence of other endocrine cells is advantageous for achieving optimal β-cell function and sufficient insulin secretion remains uncertain.

Although SC β-cells generated *in vitro* closely resemble mature human β-cells, they lack the expression of crucial maturation markers, namely UCN3, MAFA, and SIX3. Furthermore, their capacity for glucose-stimulated insulin secretion does not match that of fully mature human β-cells. The inability to fully replicate *in vitro* functionality can be attributed to a dearth of knowledge concerning the factors governing β-cell maturation during neonatal development *in vivo*. The impact of nutritional and metabolic changes on the β-cell niche, which play pivotal roles in *in vivo* maturation, remains inadequately understood and cannot be faithfully recapitulated in SC β-cell differentiation protocols. Remarkably, the expression of maturation markers becomes evident after transplantation, indicating the influence of the *in vivo* environment. Mature β-cells exhibit glucose-dependent insulin secretion, responding comparably to glucose and potassium, whereas fetal β-cells and SC β-cells demonstrate substantially lower insulin secretion in response to glucose. Furthermore, SC β-cells secrete insulin in response to amino acids, which typically fail to induce insulin secretion in mature β-cells.

These functional disparities may reflect the role of fetal β-cells in embryonic growth, wherein continuous insulin secretion is required, as opposed to mature β-cells that primarily secrete insulin postprandially. Recent investigations have shed light on the distinctions between fetal and mature β-cells in terms of glucose metabolism, mitochondrial activity, and nutrient sensing. Inducing metabolic maturation through endocrine cell clustering or the expression of mitochondrial activity regulators facilitates insulin secretion via mitochondrial oxidative respiration, a process critical for insulin secretion in mature β-cells.

These findings offer promise, as the generation of cells exhibiting heightened functionality could potentially reduce the number of transplanted cells necessary for diabetes treatment and expedite diabetes reversal.

The transplantation of SC β-cells into individuals with type 1 diabetes (T1D) faces the significant challenge of immune rejection. Physical protection through the encapsulation of SC β-cells using alginate microspheres or macrodevices has exhibited promise. Macroencapsulation devices, in combination with SC progenitor cells, have demonstrated the ability to regulate blood glucose levels in immunocompromised mice.

Encouragingly, modified alginate spheres containing SC β-cells, transplanted into diabetic rodents without the use of immunosuppressants, have achieved sustained blood glucose control through the production of human insulin.

An alternative strategy involves utilizing engineering techniques to confer immune protection. Proposed gene modifications in transplanted cells, aimed at inducing immune tolerance, include the incorporation of tolerogenic cytokines and immunomodulatory proteins such as HLA-G, PD-L1, and CTLA-4, as well as reducing HLA expression. Such modifications could enhance tolerance to β-cell antigens without adversely affecting the recipient's immune system through the administration of immunosuppressive drugs. Additionally, a complementary approach involves attenuating the T cell-specific attack on β-cells by manipulating Treg cells.

Improving the ability of β-cells to reproduce themselves

Promoting the replication or expansion of β-cells through self-replication is a potential future therapy for diabetes. β-cells remain inactive during infancy. However, certain conditions such as obesity and pregnancy can still induce β-cell replication. Different species differ in their proliferative capacities, which are dependent on their age. It is possible to stimulate the regeneration of these cells by targeting the pathways that control their growth. Signaling through the ERK pathway is enhanced when specific receptors are activated. Insulin and glucose, glucagon-like peptide-1 (GLP-1), have demonstrated the ability to trigger mitogenic signaling via the PI3K/Akt/mTOR pathway. Glucose signaling also involves the calcineurin/NFAT and ERK pathways, while GLP-1 signaling stimulates cyclic adenosine monophosphate (cAMP) generation to promote β-cell proliferation Many circulating factors, including GLP-1 from intestinal cells, osteocalcin derived from osteoblasts, and thyroid hormone, are known to promote the proliferation of cell types present in the body. The MAPK and PI3K/Akt pathways play key roles in regulating β-cell proliferation. The activation of ERK1/2 through the MAPK pathway is the main mitogenic pathway that distinguishes β-cell function from metabolic regulation, as it does not play a role in insulin secretion.

The MAPK pathway also influences the mitogenic effects of growth factors, nutrients, and hormones. The PI3K/Akt/mTOR pathway is a significant signaling pathway responsible for transmitting signals that promote β-cell proliferation. It can be activated by insulin, GLP-1, and glucose and plays a crucial role in regulating cellular processes related to growth and proliferation in β-cells.

In conclusion, these approaches offer promising avenues for future diabetic therapies, and it emphasizes the importance of understanding the pathways that regulate β-cell proliferation and the factors that influence their replication. By targeting these pathways and utilizing circulating factors such as GLP-1, osteocalcin, and thyroid hormone, researchers aim to enhance β-cell regeneration and expansion. Additionally, stem cell therapies, including the use of embryonic stem cells and induced pluripotent stem cells, hold the potential for generating β-cells and replacing damaged or lost cells.

Gene therapy is also highlighted as a potential intervention for type 1 diabetes mellitus. The ability to modify or introduce genes that regulate insulin production and glucose metabolism opens new possibilities for treatment.

Advances in gene therapy techniques, such as clustered regularly interspaced short palindromic repeats-CRISPR-associated protein 9 (CRISPR-Cas9), offer hope for precise genetic modifications to correct underlying genetic defects associated with diabetes. While these approaches show promise, challenges remain. The ethical considerations surrounding the use of embryonic stem cells and the tumorigenic risk associated with undifferentiated stem cells need to be addressed. Furthermore, the optimization of differentiation protocols and the translation of these therapies from animal models to human clinical trials are essential steps in their development, provides insights into the current treatment and approaches gene therapy as potential interventions for type 1 diabetes mellitus. Continued research and advancements in these areas have the potential to revolutionize diabetes management and improve the lives of individuals living with this chronic condition.

Role of the Microbiome

The gut microbiome plays a significant role in metabolic health, and its impact on diabetes is an area of active research.

It appears that the human oral and gut microbiota are deeply interdigitated with diabetes. It is that simple. Recent studies of the human microbiome are capturing the attention of scientists and healthcare practitioners worldwide by focusing on the interplay of gut microbiome and diabetes. These studies focus on the role and the potential impact of intestinal microflora in diabetes. We paint a clear picture of how strongly microbes are linked and associated, both positively and negatively, with the fundamental and essential parts of diabetes in humans. The microflora seems to have an endless capacity to impact and transform diabetes.

We conclude that there is clear and growing evidence of a close relationship between microbiota and diabetes, and this is worthy of future investments and research efforts.

- **Gut Bacteria:** Studies have shown that the composition of gut bacteria differs between individuals with and without diabetes. Certain bacterial strains may influence insulin sensitivity and glucose metabolism.

Recently, studies of the human microbiome are capturing the attention of scientists and healthcare practitioners worldwide by focusing on the interplay of gut microbiome and diabetes. Understanding the consequences of balance in human gut microbiota and diabetes should prove very useful in developing future promising therapeutic interventions. Diabetes is a common chronic endocrine and metabolic disease, which impacts humans globally.

Type 1 diabetes (T1D) is prevalent among children and adolescents, although the disease can occur at any age. The pathogenesis of T1D occurs when the endocrine system cannot produce insulin due to an autoimmune-mediated response leading to both inflammation and destruction of pancreatic β-islet cells. Type 2 diabetes (T2D) is a more prevalent form of diabetes most commonly occurring among adults and is usually caused by a combination of insulin resistance and an insulin deficiency.

Among the risk factors associated with diabetes are often things like a family history of diabetes, unhealthy eating habits, and obesity. The increasing prevalence of diabetes is a worldwide phenomenon following the continuous growth in urbanization, changes in diet, and the emergence of more sedentary lifestyles. According to a 2019 report, about 463 million adults worldwide currently have diabetes and future projections indicate the number of diabetic patients will reach 700 million by 2045.

According to epidemiological observations, specific changes in the diversity of intestinal microflora are one of the characteristics of diabetic patients. At the same time, there is also growing evidence of a close association between gut microbiota and diabetes.

The human gut is a complex ecosystem consisting of microbiomes, host cells and nutrients. There are about 100 trillion bacteria in the intestinal tract, and they form the gut microbiota. Gut microbiotas are composed of many diverse species of bacteria. These are taxonomically classified by genus, family, order and phylum. The intestinal microflora of healthy adults principally consists of six phyla: Firmicutes, Proteobacteria, Bacteroidetes, Actinobacteria, Fusobacteria and Verrucomicrobia. Bacteroidetes and Firmicutes occupy the dominant position in the human intestinal tract and play a pivotal role in the nutritional absorption system and support intestinal barrier enhancement. Genomic analysis of lean mice and healthy humans also confirmed the dominance of Firmicutes and Bacteroidetes, and most research indicates that Bacteroidetes outnumber Firmicutes.

Current research continues to find associations between microbiota and diabetes (T1D and T2D), and these appear to involve many metabolic effects and immune response processes, and most of these associates with more specific mechanisms. Some of the future research activities exploring gut microbiota balance variations and diabetes will lead to new interventional experiments, and potential evaluation of a causal hypothesis. This review provides an overview of studies that focus on gut microbiota balance in humans with diabetes. So far, we know there is a range of recent evidence leading to some support for the potential causal role of gut microbiota in aspects of diabetic disease. It is now clear that future research will examine the potential for and discovery of the microbiota-related underlying mechanisms of diabetes. It is only a matter of time and effort to follow the increasing evidence supporting these linkages.

The composition of the microbial community ecosystem is dynamic, and its composition is dependent upon many factors. Recent experiments using animal models indicate that intestinal microflora is regulated by factors including genes, medication, and diet. The gut microflora is easily altered by dietary changes. Experiments have shown that dietary changes can induce temporary shifts in a large number of microorganisms as rapidly as within 24 hrs. Since diet is the main source of energy for individuals and a crucial method for humans to maintain health and growth, diet composition has a big impact on gut microbiota. It therefore follows that diet is also a vital regulator of gut microbiota. Gut microbiota composition also varies with an individual’s age, and studies have shown these age-related gut microflora changes could possibly occur due to changes in diet at different ages and changes in inflammation due to some age-related diseases and changes leading to decreased immune system function. At the same time, the varying composition of gut microorganisms has been identified in disparate geographical regions and this may also be related to different regional eating habits.

The gut microflora plays a pivotal role in the body's metabolism and immunity responses can also become a regulator of the effect of diet on the host's metabolic state. On the other hand, these factors may also provide a potential impact on the onset of metabolic diseases like diabetes. The type, quality, components and source of human food intake will affect the composition of gut microbiome, as well as the functions and interactions in the microbiome ecosystem.

The main energy source of the gut microflora is dietary carbohydrates. The incidence of T2D is inversely associated with the total amount of dietary fiber intake. Dietary fiber is also found to impact intestinal microflora populations, and research indicates that fiber intake is associated with an increase in microbial diversity and the ratio of Firmicutes/Bacteroidetes. Some studies have confirmed that an increase in dietary fiber intake also increases the abundance of the human intestinal microflora and leads to higher microflora richness. Fiber intake is also associated with higher microflora stability.

Dietary fiber intake promotes the fermentation of intestinal microbes, and this appears to cause an increase in short-chain fatty acids (SCFAs). As ligands of free fatty acid receptor 2 (FFAR2) and free fatty acid receptor 3 (FFAR3), SCFAs participate in the regulation mechanism of glucose homeostasis. Propionic acid is reported to be produced mainly by threonine; glycine, glutamic acid, lysine, ornithine and aspartic acid can be used to synthesize acetate; threonine, glutamic acid and lysine acid can be used to synthesize butyric acid, of which threonine can produce three main SCFAs. Studies have reported that soluble fiber has a direct blood glucose lowering effect. Intake of soluble dietary fiber increases the viscosity of gastric juices; the more viscous fiber leads to gastric emptying times that are longer.

Additionally, these changes lead to small intestine transit time slowing, and increased starch digestion, which is associated with a reduced rate of glucose absorption, leading to changes in blood glucose and cholesterol concentrations. Consuming more dietary fiber appears to reduce the risk of T2D and is also associated with maintaining a healthy weight. Healthy adults and children can increase their intake of plant foods rich in fiber, while reducing total energy intake that is more often associated with high-sugar, high-fat, and low-fiber foods. Nevertheless, some SCFAs appear to be involved in some of the mechanisms associated with diabetes, which also establishes the link between microbiota and diabetes.

A recent study combined measurements of intestinal microbiome diversity with diet history, and blood test parameters from volunteers. These data were evaluated using machine learning algorithms to predict how an individual's postprandial blood glucose production responded to real-life diets. This indicated that a personalized diet can successfully improve postprandial blood glucose elevation. By combining these techniques and big data analysis, and the use of more specific medicinal nutrition recommendations shows the possible prevention and management of T2D with more effective personalized nutrition guidance. The widespread use of personalized nutrition also faces many challenges, such as the historic lack of reliable and repeatable results, also there are omics technology problems such as high cost, and the need for more research evidence to support actual effectiveness.

In addition to SCFAs, intestinal microflora appears to regulate lipopolysaccharide (LPS) levels and these levels are also thought to be involved in the development of diabetes. Patients with T2D have fewer butyrate-producing bacteria than non-diabetic patients. Additionally, the ratio of Firmicutes/Bacteroidetes is also significantly lower in T2D patients than in non-diabetic patients. By reviewing the results from across numerous studies, we can observe which intestinal microflora types and balances are co-occurring and possibly correlated with diabetes.

In T2D patients, there is an abundance of *Bacteroides*, *Faecalibacterium*, *Akkermansia*, and there are lower concentrations of *Roseburia*, while *Ruminococcus* and *Fusobacterium* are elevated. Gut microbiota was also reported to have a relationship with T1D in previous studies. Gut microbial communities appear to have an impact starting in infancy, and it is speculated that T1D is possibly related to the early effects of the gut microbiome.

The interaction between the human body and the intestinal microflora appears to start at birth, and the development of the gut microbiome then evolves and goes through three fundamental stages: The first is a developmental stage (occurring during months 3-14), the second is a transition stage (occurring during months 15-30) and finally the third stage is a stable period (occurring during months 31-46).

Abnormal gut microbiota is often observed in pre-diabetic patients. A controlled study was conducted to analyze 134 Danish patients with prediabetes. When these subjects were compared with normal controls, the intestinal microflora of patints with prediabetes showed abnormal characteristics, with low concentrations of *Clostridium* and mucin-degrading *Akkermansia muciniphila*. In another study, vertical stool samples from 903 children aged 3-46 mo were analyzed, and the study found that early intestinal microorganism ecology is impacted by breastfeeding and childbirth. The full implications of these observations, although not conclusive, appear to indicate that there is a developmental impact on microbiome development and the strength and outcome of these factors will need to be more fully explored in future research.

The mouse model is commonly used in the study of intestinal microflora, and the function of the intestinal microflora can model that for mammals. Studies using mice as models provide important insights and help to build an understanding of the relationship between the intestinal microflora and diabetes. Mice are generally used as the preferred model for research, because the intestinal structures of mice and human subjects are quite similar.

These models can also provide an evaluation of experiments designed to disturb the intestinal microbiota using controlled experimental apparatus. Closer observations of the microbiota composition are helpful in identifying and evaluating the potential causal relationships and possible mechanism of the interaction between host and intestinal microorganisms. Although there is more work to be accomplished here, it is expected that a better understanding of how these balances in microbiota impact both health and diabetic disease processes will be forthcoming.

It is important to note that previous research indicated that when mice do not have gut microbiota (germ-free mice) they also have lower body fat and insulin resistance than conventional mice, and the tolerance of insulin and glucose in germ-free mice was higher than that observed in routinely fed mice. This study also paved the way for the examination of many potential mechanisms in the past decade.

This was followed by a subsequent intestinal microflora transplantation experiment, and the germ-free mice that received transplanted gut microflora from ob/ob mice showed a significant increase in obesity with associated insulin resistance. In subsequent weight-loss surgery experiments, the correlation between obesity and intestinal microflora was also demonstrated, with an observed increase in fat mass in germ-free mice transplanted with altered microbiome.

In a recent study, the Koch hypothesis was a useful method to examine the possible causal link between gut microflora and obesity. These studies all started to substantiate the potential cause-and-effect relationship. However, the results of gut microbiological studies in mouse models cannot be simply directly translated into human comparisons and these pitfalls of direct comparisons need to be avoided until more evidence from human studies can be completed to evaluate any potential causality.

Studies in mouse models support the hypothesis of potential causality between gut microbiota and the development of obesity and diabetes, but so far there has been little research completed related to causality in human subjects. The reproducibility of human experimental studies is also sometimes limited, which may also be influenced by variations in differences among study settings, geographic locations of sample preparation, as well as inconsistencies in data analysis. Moreover, there are some studies which have produced contradictory observations and data in human research. It is unclear, as to the root cause of this variation; however, it may be partially attributed to different dietary habits and environmental/cultural factors around the world as well as to different experimental methods used. However, future conclusions regarding human microflora connections to diabetes will require intervention studies to determine if there is a causal relationship with microflora as a driving factor for disease development. To date, fecal microbiota transplantation (FMT), antibiotic therapy, diet, and probiotic therapy are considered effective in various intervention studies.

Contemporary research shows that FMT has also been considered an effective tool to gain evidence of microbiome association and the causality of many diseases. In a randomized, double-blind controlled experiment of insulin-resistant men, patients received gut microbiota from lean body mass donors, and analysis of the experimental results demonstrated that FMT improved insulin sensitivity and the number of butyrate-producing bacteria also increased significantly. However, not all patients receiving FMT from lean donors experienced the same beneficial effects, and more research is required for comparative analysis.

Metformin

Forslund et al proposed that changes in gut microbiome in diabetic patients are not entirely endogenous and can be explained in a large part by metformin treatment. Upregulation of glucagon-like peptide-1 (GLP-1) and peroxisome proliferator-activated receptors has been reported in healthy individuals and in T2D patients after metformin treatment. Metformin is also an insulin hormone regulator that has multiple effects in the intestine, such as increasing GLP-1 concentration in the intestine and extraction of glucose.

Metformin can reduce lipid absorption and inflammation caused by LPS and can also reverse T2D-related changes because the abundance of several gut microbiota appears more like non-diabetic control levels when treated with metformin.

Recent studies have shown that metformin disrupts the microbial characteristics associated with diabetes, including changes in the composition of the intestinal microflora. A double-blind, placebo-controlled experiment of T2D patients showed that metformin altered the intestinal microflora balance in treatment-naive T2D patients, while germ-free mice had glucose tolerance after receiving metformin-modified microbiota and showed improved results. Metformin was used in a controlled experiment in mice fed a high-fat diet (HFD), and the results showed that the abundance of the mucin-degrading bacteria Akkermansia muciniphila (*A.* muciniphila) was higher than that observed in the control group. Similar conclusions have been found in other human studies. A recent study analyzed the gut microbiome of Chinese T2D patients receiving different anti-diabetes drugs, and metformin recipients showed enrichment of Turicibacter and *Spirochaete*. Another study used genomic analysis to analyze the composition of intestinal microflora in diabetic patients taking metformin. The results showed that *A.* muciniphila and several SCFAs-producing microbiotas were low when compared to non-diabetic patients who had a relatively high abundance, and this study revealed some of the mechanism by which metformin changes the composition of intestinal microflora by enriching *A.* muciniphila and several SCFAs-producing microbiotas.

Probiotics and intervention experiments

Probiotics appear to have a wide range of effects on the host, including improved regulation of insulin sensitivity, which may also be related to host metabolism mediated by the gut microbiome balance, by improving host metabolism composition, by reducing pro-inflammatory cytokines, and by reducing intestinal permeability. In addition, probiotics have the potential to directly improve host metabolism and increase SCFAs production. Supplementing probiotics can also improve intestinal balance through the production of antibacterial compounds and competition with pathogens. Probiotics may also regulate the host's immune response, and activate specific gene activation and impact extra-intestine processes and disorders.

Numerous experiments in mouse models and human experiments have confirmed that multiple probiotics reduce insulin resistance by affecting gut microbiota and consequently, may influence health. Preliminary studies have shown that ingestion of fermented dairy products such as yogurt can transport lactic acid bacteria to the gut, alter gut microbial composition, inhibit the production of LPS, and increase the close connection of gut epithelial cells. At the same time, a prospective, double-blind, randomized trial of 21 people with high glucose tolerance showed that oral administration of *Lactobacillus* reuteri also improved insulin secretion.

Recently, *A*. muciniphila has been frequently mentioned in current studies, and these studies show it reduces insulin resistance and reduces destruction of the intestinal barrier. *A.* muciniphila was reported to be less abundant in pre-diabetic patients, as well as among newly diagnosed T2D patients, suggesting that the low levels of *A.* muciniphila may be a biomarker for impaired glucose tolerance. A recent study found that *A.* muciniphila-derived extracellular vehicles (AmEVs) can regulate gut permeability. The analysis of fecal samples revealed that AmEVs levels were low in T2D patients. Moreover, in a study of diabetic mice, the administration of AmEVs was associated with an observed decrease in fat content and an increase in glucose tolerance in diabetic mice. Studies in mouse models have shown that supplementation with *A.* muciniphila can reduce low-grade inflammatory responses and metabolic disorders. In another study of HFD mice, Akkermansia was reported to be associated with reduced LPS levels, which may be related to the ability of Akkermansia to maintain mucus layer thickness, which reduces intestinal permeability and LPS leakage. *A.* muciniphila is a mucus-degrading bacterium, and its abundance is negatively correlated with glucose tolerance and fat accumulation in mouse models, but more evidence needs to be acquired in human studies to establish clear results. The mechanism of decreasing insulin sensitivity of *A.* muciniphila may also be related to its membrane protein. Amuc_1100 is a special membrane protein isolated from *A.* muciniphila. Studies have shown that the special protein binds to Toll-like receptor 2 (TLR2) and participates in the protective mechanism of the intestinal barrier.

Clinical experiments are increasing in frequency and new results are encouraging. A recent randomized, double-blind placebo trial of 40 insulin-resistant adults who were orally supplemented with *A. muciniphila* showed that it played a role in reducing biomarkers associated with inflammatory responses, these biomarkers have also been linked to diabetes. Experiments have also shown that *A. muciniphila* improves insulin sensitivity in patients.

However, the regulatory effects of probiotics on improving insulin sensitivity have population limitations and may not work for everyone. It is worth noting, for example, that two recent studies have shown that probiotics have no effect on gestational diabetes as this disorder appears entirely hormonal.

METABOLIC PRODUCTS AFFECT THE UNDERLYING MECHANISMS

Obesity and T2D are often characterized by changes in intestinal microflora, inflammation, and disruption of the intestinal barrier. Chronic, low-grade inflammatory response is a common characteristic of T2D and obesity, and this systemic inflammatory response is also thought to drive insulin resistance. Previous research in mouse models has confirmed that the intestinal microflora is responsible for the increased inflammatory response in obese patients[28]. Furthermore, the gut microbiome can interact with dietary components and habits to influence host insulin sensitivity, intestinal permeability, glucose and fat metabolism[56]. The gut microbiota has long been regarded as a virtual organ of human metabolic activity[57], and its metabolic activity interacts with insulin resistance and diabetes.

Gut microbial metabolites can affect host physiological functions. Metagenomic analysis showed that the intestinal microflora of T2D patients and healthy individuals is often markedly different, and the decline in butyrate-producing bacteria may be the cause of impaired glucose metabolism. Modification of gut microbiota caused by external interventions such as diet leads to dysregulation and secretory changes of intestinal microbial metabolites, triggering a variety of potential mechanisms leading to insulin resistance and diabetes. At the same time, intestinal microflora can also affect metabolism and the potential risk of diabetes by changing the way they respond to dietary ingredients. There are many ways to interact with the host and intestinal microorganisms, and in the past decade, many studies were conducted to understand mechanisms for the analysis and hypothesis of microflora involved in regulating insulin resistance, including LPS and SCFAs. Most of the studies have focused on triggering the markers of diabetes: A low-grade inflammatory response and an immune response, in which intestinal microflora and its metabolites play a key role.

LPS

LPS is reported to induce inflammatory cytokines through immune cells and adipocytes, causing low-grade inflammation, while acetic acid or butyrate can regulate the function of immune cells. According to Gram staining analysis, the two most common phyla in clinical classification belong to different groups, namely Gram-positive bacteria and Gram-negative bacteria. LPS is derived from the cell wall of Gram-negative bacteria. The LPS of gut microbiota binds to Toll-like receptor 4 (TLR4), then it initiates a signal cascade with good characteristics, inducing the inflammatory response and the expression and secretion of cytokines. The TLR4 signaling pathway is considered to be one of the main triggers of the obesity-induced inflammatory response. Studies have shown that saturated fatty acids can cause insulin resistance and low-grade inflammation by activating the TLR4 signaling pathway. At the same time, different studies have shown that TLR2 is also involved in the inflammatory response when the signaling cascade caused by LPS-LBP-TLR4 is activated. The integrity of the gut barrier seems to play a crucial role in the development of obesity and T2D.

The intestinal epithelium acts as a barrier, and its basic function is to limit the interaction between the intestinal microflora, the basic local immunity and other parts of the body. The integrity of the gut barrier can maintain the functional balance of the mucosa, which can be maximally absorbed while maintaining an effective defense response. Increased production of LPS by the intestinal microflora will also activate the endocannabinoid system. In addition, too much LPS may destroy the integrity of the intestinal barrier and increase LPS absorption. Animal studies have indicated that LPS is involved in the regulation of diabetes-related mechanisms, which can be characterized by the occurrence of increased inflammatory response.

SCFAs

SCFAs are composed of acetic acid, propionic acid and butyric acid. The deficiency in SCFAs is thought to be associated with T2D. Currently, studies have shown there is confirmation that SCFAs have a protective effect on the gut barrier, and result in a decrease in the number of butyrate-producing bacteria that may lead to changes in intestinal permeability. Studies have shown that butyrate can promote the expression of tight junction proteins and affect the mucosal barrier function, while acetate has also been reported to have a good performance in reducing mucosal permeability and enhancing the intestinal barrier function. The SCFAs mechanism involves activation of G proteins of the L-cells to promote the release of GLP-1 and peptide YY (PYY) to regulate glucose homeostasis, and at the same time, the SCFAs also effect the intestinal barrier, up-regulate 5'-AMP activated in muscle and liver tissues and the protein kinase signaling pathway, which are related to insulin resistance and inflammation, and oxidative stress may have a potential role.

Clinical studies have shown that dietary fiber promotes SCFAs production by gut microorganisms, while most other potential producers are relatively reduced in T2D patients. In a recent study, intestinal microflora before and after dietary fiber interventions in volunteers were transplanted into germ-free mice.

The study indicated the strong and significant association between gut microbiome and improved fiber glucose-induced host glycemic control.

At the same time, the study proposed that when the SCFAs-producing bacteria promoted by dietary fiber have greater abundance and diversity, participants' glycated hemoglobin levels were improved. On the other hand, SCFAs activate the vagal afferent neurons, which establish a connection between the intestinal information and the brain. This connection has been proved to play a role in controlling human feeding behavior, which also raises new considerations for the potential mechanism of SCFAs in increasing the risk of diabetes by controlling human feeding behavior and selection of dietary response.

In a recent study, genome-wide genotyping, intestinal genomic sequences, and fecal SCFAs level information from 952 normal blood glucose individuals were synthesized. A two-way Mendelian randomization (MR) analysis was used to assess causality, and the results showed that butyrate and propionate were proved to be involved in a causal relationship with diabetes, with oral glucose tolerance test showing a positive correlation between butyrate and improved insulin resistance and between malabsorption of propionic acid and the incidence of T2D, which offers evidence for the causal effect of gut microbiota on metabolic characteristics.

Butyrate

In a fecal bacteria transplantation experiment, insulin resistance patients received fecal microflora from insulin-sensitive donors, which resulted in a significant improvement in insulin sensitivity with increased abundance of butyrate-producing bacteria. Through the analysis of human fecal samples, *Faecalibacterium prausnitzii* (*F. prausnitzii*) was found to be the main butyrate-producing bacteria. The abundance of *F. prausnitzii* and *Roseburia* in intestinal microflora of T2D patients is lower than that of healthy individuals, according to large scale metagenomic association studies in different populations. Other studies have also demonstrated that the enrichment of *F. prausnitzii* can reduce inflammatory symptoms and insulin resistance. *Roseburia spp*. is also a butyrate-producing bacteria, which has a pivotal part in maintaining intestinal health and immune defense. It can regulate the dynamic balance of T cells by producing butyric acid. Butyrate has a protective effect on the intestinal barrier by inducing the synthesis of mucin, it reduces the intestinal permeability and prevents bacteria from passing through. Butyrate also acts on the colonic epithelium, reducing oxidative stress and inflammation. In addition, the abundance of butyrate-producing bacteria is lower in prediabetic patients than in healthy people, which may indicate that the absence of butyrate-producing bacteria is one of the precursors of diabetes.

Bile acids and branched-chain amino acids

Bile acids are synthesized in the liver and are transformed into secondary bile acids through the enzyme metabolism of gut microbiota. In an experiment on rats, the intestinal microflora of oral bile acid treated rats was analyzed and showed there were significant changes in phylum levels and an increased ratio of Firmicutes/ Bacteroidetes. Secondary bile acids are associated with the regulation of insulin sensitivity through activation of Farnesoid X receptor (FXR) and the Takeda G protein-coupled receptor 5 (TGR5) receptors. A study reported reduced genetic and diet-induced insulin resistance in FXR knockout mice.

FXR activation induces increased secretion of fibroblast growth factor 19 (FGF19 in humans, FGF15 in rodents), which improves glucose tolerance and insulin resistance. Activation of the TGR receptor stimulates intestinal L cells to secrete GLP-1, thereby improving insulin sensitivity.

Branched-chain amino acids (BCAA) are thought to be related to the risk of developing T2D and are considered to be predictive markers for T2D. Several studies have reported decreasing plasma BCAA levels in T2D patients.

A large cohort study also demonstrated the strong association between BCAA and diabetes, as well as the potential role of amino acid metabolism in the early stage of diabetes. Studies in rats have demonstrated that high-fat dietary supplementation with BCAA also leads to insulin resistance.

Human studies have confirmed the conclusion that supplementing BCAA in diet increases the risk of T2D and insulin resistance. In a recent study, patients with T2D received a short-term dietary supplement of BCAA, which showed reduced insulin secretion after a meal and changes in the composition of the intestinal microflora. The synthesis pathway of BCAA has been shown to be related to *Prevotella copri* (*P. copri*) and *Bacteroides vulgatus* in intestinal microflora. Subsequent experiments showed increased BCAA levels and increased insulin resistance in germ-free mice transplanted with *P. copri*. The mechanism of BCAA inducing insulin resistance has been proposed to be attributed to the increased oxidation of free fatty acids and the activation of phosphatidylinositol 3-kinase (PI3K). However, the exact mechanism is still unclear and needs further study.

GUT MICROBIOTA AND T1D

Both T1D and T2D are associated with complex immune system and gut microbiome interactions. Gut microbiota disorders are associated with the pathogenesis of T1D, and the incidence of T1D is related to the interaction of gut microbiota and innate immunity. Non-obese diabetic (NOD) mice have developed into the prototype model of T1D. The occurrence of T1D in NOD mice depends on the composition of gut microflora and LPS-mediated gut signals involving TLR4 and MyD88. MyD88 is a key signal transduction factor in interleukin (IL)-1 and TLR signal transduction pathway.

Its defect alters the composition of distal intestinal microflora. Studies have reported that NOD mice lacking MyD88 protein will not develop T1D. In the follow-up study, the gut microflora of MyD88-deficient NOD mice protected by diabetes was transferred to wild-type NOD female mice, which reduced the intensity of pancreatitis and significantly delayed the occurrence of autoimmune glycosuria.

The gut microflora of preclinical T1D patients is characterized by the dominance of Bacteroidetes, the lack of butyric acid-producing bacteria, and the decrease of bacterial and functional diversity. A study in which colonic bacteria released large amounts of acetic acid or butyrate by feeding NOD mice with specific foods found that the key characteristics of the disease were negatively correlated with the concentrations of butyrate and acetate in blood and feces.

The mechanism is believed to be that the acetate diet reduces the frequency of autoimmune T cells in lymphoid tissues, while butyrate diet increases the number and function of regulatory T cells. Human studies have also shown that SCFAs are involved in the prevention mechanism of early-onset human T1D. A recent prospective study demonstrated the protective effect of SCFAs on early-onset human T1D. This study analyzed 10913 metagenomes from 783 stool samples, and increased several bacterial pathways that promote SCFAs biosynthesis was found in healthy controls.

However, unlike T2D, transfer of the whole microbiota may not reduce the incidence of T1D. Recently, a study investigated the incidence of T1D in two NOD groups with different gut microbiota. Afterwards, 16S rRNA gene sequencing was used to analyze the gut microbiota with high or low incidence of T1D in the two groups of NOD mice, and the high incidence population was colonized with the microflora of the low incidence population. The results showed that the gut microbiota changed but the incidence of diabetes did not. In another study, germ-free mice received fecal microflora from children with loss of β-cells, the result of which indicated that loss of β-cells after human T1D onset cannot be converted in germ-free NOD mice by FMT. However, it is interesting that single symbiotic bacteria, such as *A. muciniphila*, can be used as probiotics to reduce the incidence of diabetes.

LPS also participates in the regulation of autoimmunity, most of which are *Escherichia coli* LPS involved in suppressing innate immune signals, but *Bacteroides dorei* LPS does not show significant improvement in T1D incidence. In a recent study, intraperitoneal injection of *Escherichia coli* LPS in T1D mice showed a decrease in the incidence of T1D and an improved autoimmune response, while another study of NOD mice that received oral injection of *Escherichia coli* LPS also demonstrated an improvement in local immunity. The concept that the pathogenesis of T1D is affected by gut microbiota has been well established in mouse models, but human studies on the microbiome in T1D are still few and far between to provide convincing evidence.

Gut microbial colonization in fetuses and infants can lead to dynamic changes in diversity, which may further affect disease susceptibility. A study of 33 infants with T1D genetic predisposition observed a significant decrease in alpha diversity among T1D progenitors, along with peaks in inflammatory organisms, gene function, serum and fecal metabolites, and this diversity difference occurred after serum conversion and was determined to be specific to T1D.

The pre-clinical T1D patients' intestinal microflora is characterized by a dominant Bacteroidetes, with low stability and diversity of intestinal microflora. Studies have shown that these changes were found after the body produced auto-antibodies, which could indicate the role of gut microbiota in the autoimmune process, while the triggering mechanism of T1D disease was not determined.

There is growing evidence that islet autoimmunity is the first stage of T1D. Islet autoimmunity refers to the continuous existence of islet antigen autoantibodies, which usually begin in early childhood.

The role of gut microbiota in activating T1D is still a very vague concept, current studies have few observations or evidence to support the explanation that gut microbiota activates T1D, and most studies focus on the involvement of gut microbiota in the β-cell autoimmunity process. The causal relationship between intestinal microflora and T1D is still unclear, because most studies are only observational studies, and lack specific mechanical and intervention.

ORAL MICROBIOTA: ANOTHER FACTOR OF GUT MICROBIOME AND DIABETES

As the starting point of the digestive tract, the importance of oral microbiota and its association with the intestinal microbiota are receiving increasing attention. The oral cavity serves as an endogenous reservoir for gut microbial strains, and oral-fecal transmission is an important process that shapes the gastrointestinal microbiome in both health and disease. Oral bacteria can translocate to the gut and lead to changes in its microbiota and possibly immune defense.

It has been recognized that oral microorganisms may cause diseases mainly by a synergistic or cooperative way, and oral diseases (*e.g.*, caries, periodontal disease) and T2D appear to be mutually correlated. Studies have reported significant differences in oral microbiota between patients with T2D and non-diabetic patients. Oral microbial biomarkers have been identified for T2D screening, diagnosis and prognosis. Recently, researchers provided a possible mechanism for the improved understanding of how diabetes increases the risk and severity of tooth loss. Diabetes may cause changes in oral bacterial composition, and the oral microbiota of diabetic mice was found to be more pathogenic in studies transplanting to germ-free mice. These studies suggested that oral microbiota is an important factor in the development of diabetes, and on the other hand, oral microbiota is also an important avenue for diabetes to cause other oral or systemic complications. This new area of investigation may represent another pathway for the oral-gut axis to potentially cause an increase in diabetic disease and deserves more in-depth research moving forward.

The current research into gut microbiome in the field of diabetes has gradually moved step by step from the initial correlation studies, which proved a strong association, to exploring the causality and potential mechanisms (Figure (Figure1).1).

It is very clear that as science looks to the future this will be a very promising frontier. It can be foreseen that the gut microbiota will be used not only as a biomarker for diabetes, but also as a target for potential therapeutic treatments. Through the intervention of gut microflora, it will eventually be possible to achieve a more precise and personalized diagnosis as well as treatment of diabetes (Table (Table1).1). This is only going to be possible with a significant investment in extensive multicenter, longitudinal, interventional and double-blind randomized clinical trials. Additionally, these will yield an extensive knowledge base upon which data science and exploration can occur. The scientific research community must proceed with a sense of urgency, if these data are to be used to their fullest advantage, as many new discoveries are waiting just ahead.

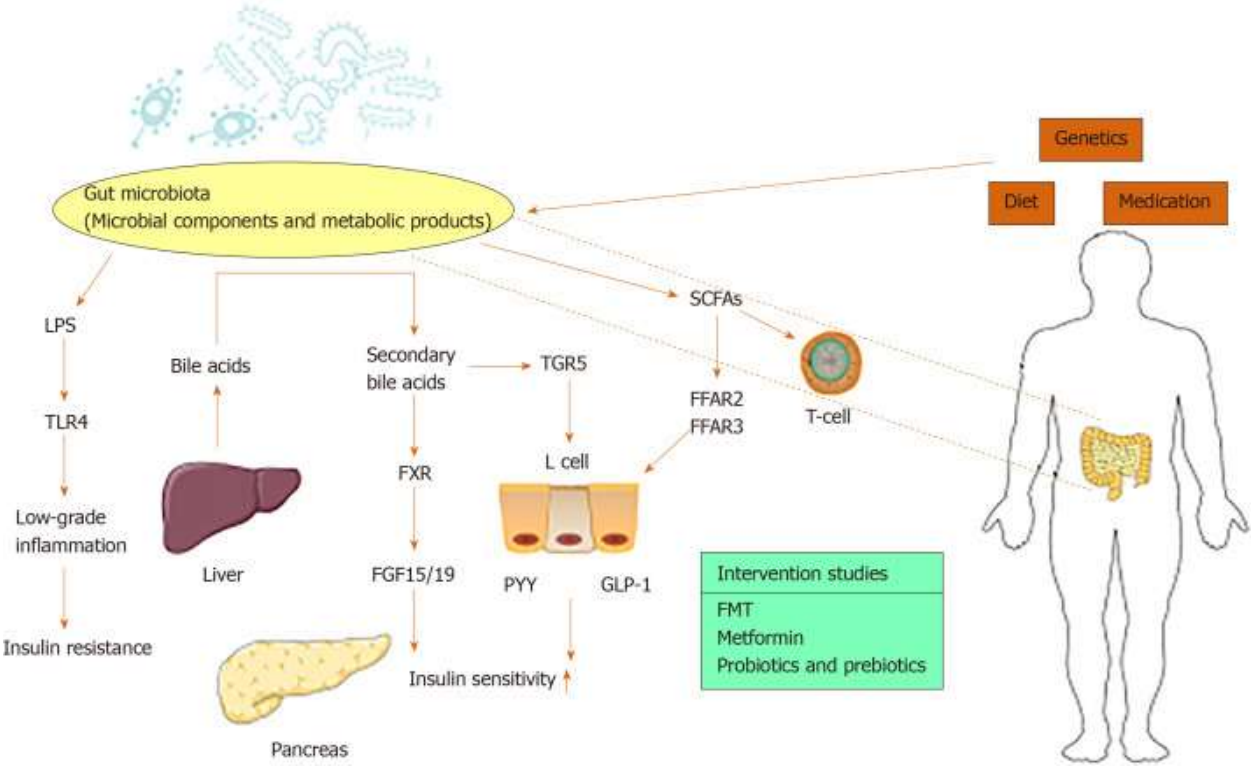
Table 1

A summary of products of gut microbiota and their mechanism of action

Gut microbiota products		Source	Mechanism	Function		Ref.
LPS		The cell wall of Gram-negative bacteria	Activates the receptor TLR4	Increase the occurrence of inflammatory response		[59,60]
SCFAs	Acetate	Carbohydrate fermentation	Activates the receptor FFAR2	Reduce the frequency of autoimmune T cells in lymphoid tissues	FFAR2 and FFAR3 stimulate the release of GLP-1 and PYY, which improve insulin secretion.	[15,91,105]
	Propionate		Activates the receptor FFAR2 and FFAR3	Promote intestinal gluconeogenesis		
	Butyrate		Activates the receptor FFAR3	Increase the number and function of regulatory T cells		
Bile acids		The microbiota from host cholesterol	Bind to the receptor	Improve insulin sensitivity		[74,76]

BCAA	*Prevotella copri* and *Bacteroides vulgatus*	TGR5 and FXR Activate PI3K and increase the oxidation of free fatty acids	Increase the risk of insulin resistance	[86,87]

LPS: Lipopolysaccharide; TLR4: Toll-like receptor 4; SCFAs: Short-chain fatty acids; FFAR 2: Free fatty acid receptor 2; FFAR 3: Free fatty acid receptor 3; GLP-1: Glucagon-like peptide-1; PYY: Peptide YY; TGR5: Takeda G protein-coupled receptor 5; FXR: Farnesoid X receptor; BCAA: Branched-Chain Amino Acids; PI3K: Phosphatidylinositol 3-kinase.



Growing evidence suggests that the gut microbiome (GM) is a critical mediator in the development of T2DM. GM is a complex and dynamic microbial ecosystem and the number of gut microbes in the intestineisestimated to exceed 10^1. Importantly, GM plays a critical role in many human physiological and pathological processes, including metabolism, immunity, tumor metastasis and inflammation. Disruption of the GM balance frequently initiates a pathological cascade increasing risk for the development of various diseases, such as diabetes, obesity, food allergies and malignancies. Specifically, dysbiosis of the GM significantly affects glucose metabolism. The diversity of dominant microbiota, and the relative abundance of microbiota were found to be different in patients with T2DM compared with controls Thus, an appropriate balance between the host and GM appears to be essential for maintaining glucose metabolism.

Experimental studies and human clinical trials have shown positive effects of various prebiotics and probiotic strains on metabolic control of patients with T2DM. These compounds appear to reverse dysbiosis and restore the gut's functional integrity. Fecal microbiota transplantation (FMT) has been shown to be safe and well-tolerated, can significantly alter the recipient GM composition (eg, by increasing butyrate-producing bacterial strains) and can affect glucose control in subjects with metabolic syndrome based on baseline microbiota. Importantly, recent research reports that FMT stabilized residual beta cell function in subjects with new-onset type 1 diabetes mellitus, further supporting the potential benefits of FMT therapy in patients with diabetes. However, the pathophysiological mechanisms underlying the effects of FMT on T2DM remain not well understood.

Immunology and Autoimmune Aspects

Immunological research is shedding light on the autoimmune mechanisms underlying type 1 diabetes.

- **Autoimmune Triggers:** Identifying environmental and genetic factors that trigger the autoimmune response leading to type 1 diabetes. Viral infections and early-life exposures are areas of focus.

  The progressive increase in T1D incidence over the years points to the role of environmental factors in triggering or accelerating the disease process which develops on a highly multigenic susceptibility background. Evidence that environmental factors induce T1D has mostly been obtained in animal models.

In the human, associations between viruses, dietary habits or changes in the microbiota and the development of islet cell autoantibodies or overt diabetes have been reported. So far, prediction of T1D development is mostly based on autoantibody detection. Future work should focus on identifying a causality between the different environmental risk factors and T1D development to improve prediction scores. This should allow development of preventive strategies to limit the T1D burden in the future.

Pathogenesis

T1D is a T-cell mediated disease that is likely driven by events occurring at the islet level, i.e. danger signals (**Figure 1**) . Therefore, autoantigens are processed and presented by dendritic cells issued from the islets that migrate to satellite lymph nodes where they drive the clonal expansion of autoantigen-specific $CD4^+$ T-cells and secondarily $CD8^+$ T-cells and B-cells.

Along with their activation, T and B-cells modify their expression of homing genes and migrate back to the islets where they expand and mediate β-cell destruction. Other potential players are currently being investigated such as FasL-expressing B cells and dual expresser (DE) cells.

Autoantigens recognized by T-cells include the four main autoantigens corresponding to those targeted by autoantibodies and chromogranin, islet-glucose-6-phosphatase catalytic subunit-related protein (IGRP), islet amyloid polypeptide and glial fibrillary acidic protein. Anti-insulin is the first antibody to be detected in patients at risk for T1D. Preproinsulin (PPI) epitopes that are presented by different HLA class I molecules to $CD8^+$ T-cells and by HLA class II molecules to $CD4^+$ T-cells have been characterized.

They span along the whole sequence of proinsulin, the insulin prohormone precursor and within the 24 amino acid signal peptide sequence of the protein. The role of insulin as a major autoantigen has been demonstrated in the non-obese diabetic (NOD) mouse, as the knockout of the *insulin 1* gene prevents the development of type 1 diabetes while the knockout of the *insulin 2* gene accelerates the disease process. PPI-specific $CD8^+$ and $CD4^+$ T-cell are detected in the peripheral blood and in islets in the mouse and in the human. A missing piece of the puzzle is the triggering event that leads to increased class I expression, expression of interferon α and homing genes and dendritic cell activation and migration.

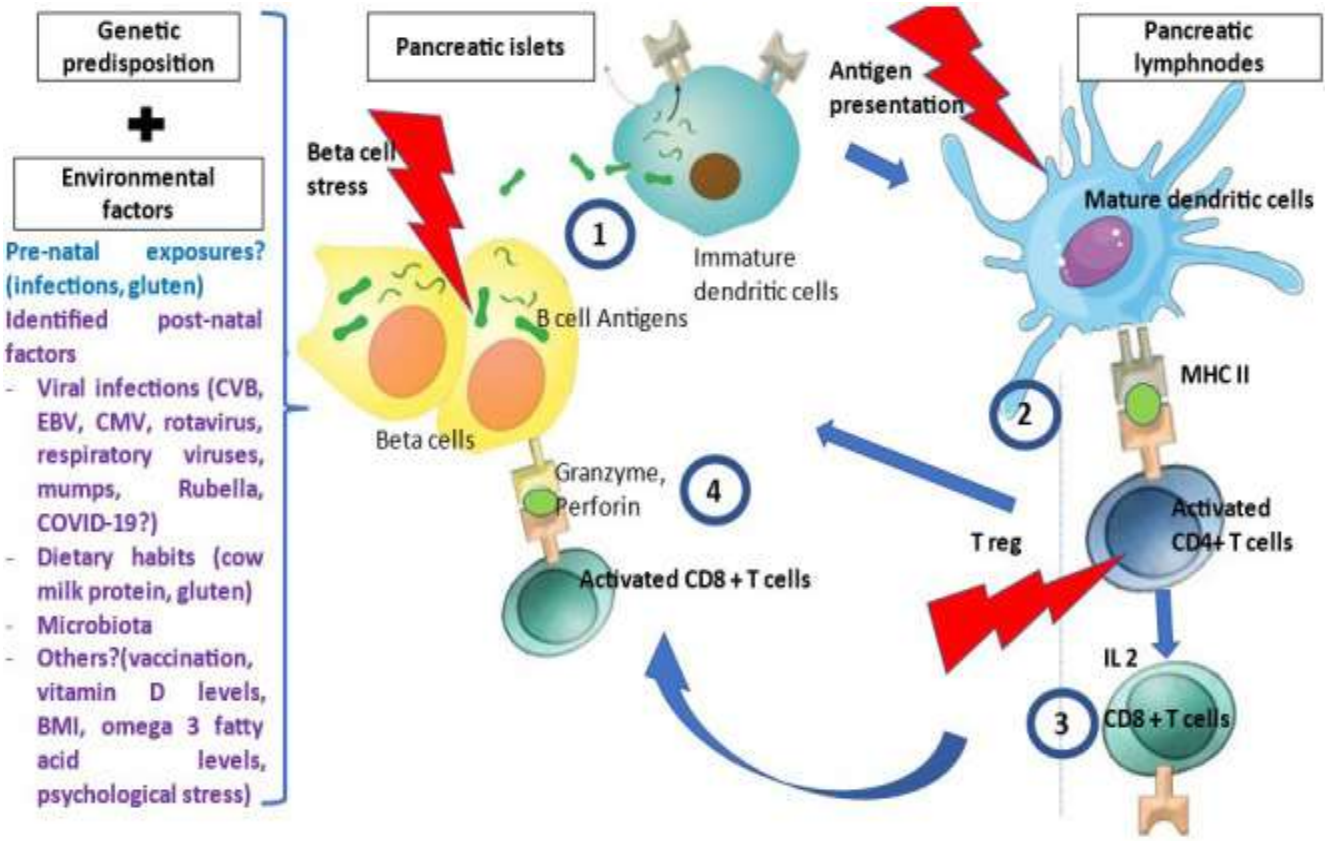


Figure 1

Pathophysiology of T1D. Many environmental factors were associated with T1D development. The initial mechanism that triggers autoimmunity is unknown. In genetically susceptible patients, in the presence of environmental factors, β cells are stressed and release β cell antigens. **1-** β cell autoantigens are processed by APCs and presented by HLA class II MHC molecules to the naïve CD4+T-cells in the peripheral LN. **2-** CD4+ T-cells are activated and polarized towards a TH1 phenotype releasing cytokines, among which IL 2, INF gamma and IL-4 at the expense of regulatory T cells (T reg). **3**- This will activate and generate auto-reactive CD8+ T-cells, which recognized autoantigen peptides presented by HLA class I MHC molecules, migrate to the islets and liberate cytotoxic granzyme and perforin to destroy β cells.

If one except rare monogenic forms T1D is a multifactorial disease that involves 60 gene variants that have been associated to T1D along with multiple environmental factors. Investigating the role of these factors in prediabetes and diabetes is complex and requires longitudinal studies as well as separate analysis for the two conditions. Monozygotic twins show a 30 to 50% concordance for T1D, pointing again to the role of environmental factors.

Individuals with an affected first degree relative have 15 times higher lifetime risk of developing T1D as compared with the general population (5% v/s 0.3%). %)

GWAS studies identified over 60 genes associated with T1D susceptibility. These genes operate both in pancreatic β cells and innate and adaptive immune systems. Variations in genes involved in central or peripheral tolerance can explain the risk of immune tolerance failure in susceptible individuals. The bioinformatic approach gave us a new way to identify culprit genes by focusing on functional aspects. Fine mapping data identified T1D associated loci in lymphocytes' selection, activation, and regulation. Genes that confer the highest susceptibility are class II HLA genes, followed by *INS*, *CTLA4* and *PTPN22* genes . Different genes are associated with different stages of T1D, and some genes are likely to influence disease progression rather than their initiation.

HLA genes contribute to 40-50% of the T1D lifetime risk. HLA class II molecules are involved in the initiation of T1D and HLA class I molecules are more likely contributing to disease progression. By activating $CD4^+$ T-cells, HLA class II-peptide complexes initiate the autoimmune response. Among class II genes, HLA-DQ alleles carry the highest susceptibility. Susceptibility is attributed to the presence of a non-aspartic amino acid in position B57 in the HLA-DQB1 pocket 9 and in positions 13 and 71 in the HLA-DRB1 chain. An odds ratio (OR) of 10 is associated with DR4-DQ8 (DQA1*03:01-DQB1*03:02) haplotypes and a lower risk with DR3-DQ2 (DQA1*05:01-DQB1*02:01 haplotypes. In addition to HLA class II susceptibility genes, several haplotypes confer a dominant protection, in particular the DRB1*15:01 (DR15)-DQA1*01:02-DQB1*06:02 (DQ6) haplotype through all stages of T1D.

The association of different HLA alleles with T1D risk modulates the risk; combinations of HLA alleles can have additive or subtractive effects leading to an increase or a decrease in the T1D risk. Heterozygous HLA-DQ2/8 genotypes confer the highest risk for T1D with OR that reach 40. The HLA-DQ6/8 (DQA1*02:01-DQB1*06:02/DQA1*03:01-DQB1*03:02) genotype is protective (OR of 0.2) . The mechanism involved in HLA-DQ6 protection remains unknown. Recent publications demonstrate the complexity of HLA gene associations with the observation of autoreactive $CD4^+$ T-cells restricted to HLA-DQ8 trans dimers that form in HLA-DQ2/-DQ8 heterozygous individuals. Children with heterozygous DR3-DQ2/DR4-DQ8 or homozygous DR4-DQ8 genotypes and a family history of T1D are four times more at risk to develop islet autoimmunity than children with the same genotypes but no T1D family history in addition to HLA class II genes, several HLA class I alleles confer a susceptibility.

Non- HLA genes provide additional risk for T1D with lower odds ratios. In the TEDDY Cohort, 5806 subjects were genotyped for 176586 SNPs (33). Nine non-HLA genes including PTPN22, Ins, SH2B3, PxK5 were identified as increasing the susceptibility to T1D.

Some of the identified gene's function in β cells while others are involved in the regulation of immune responses or responses to viral infections (PTPN22, IFIH1). A VNTR located 5'of the *INS* gene (IDDM2) on chromosome 11p15.5 is the second most strongly associated locus with T1D risk. It regulates insulin expression in the pancreas and the thymus. Long and short VNTR are associated with high and low transcription of proinsulin mRNA, respectively, in thymus epithelial cells.

A low expression of insulin may favor thymic selection of $CD4^+$ T-cells recognizing autoantigens. The protein Tyrosine phosphatase non receptor *PTPN22* gene on chromosome 1p13 encodes lymphocyte specific tyrosine phosphatase (LYP) which downregulates TCR signaling, inhibiting T-cell activation. A gain of function mutation in this gene may enhance T-cell suppression, leading to a decreased number and function of Treg cells and T1D susceptibility. *CTLA4* encodes for cytotoxic T-lymphocyte-associated protein 4 (CTLA 4) which acts as a costimulatory receptor on $CD4^+$ T-cell and inhibits their activation by binding to B7. A decreased expression leads to increased T1D susceptibility. The inducible T-cell COStimulator (ICOS, CD278) gene is expressed on activated $CD4^+$ T-cells.

It produces a stimulating T-cell activation signal and is involved in the control of regulatory CD4+ T-cells. The **A946T variant of the** Interferon induced with helicase C domain *IFIH1 (MDA5)* encodes an innate immune receptor that senses viral RNA, induces an interferon mediated virus resistance and **increases the risk for autoimmunity.** Among other genes reported as susceptible genes, STAT 4, IL2, SUMO4, IL2RA have all been involved in T-cell regulation.

The lack of full concordance between homozygotic twins, the increasing incidence of T1D over the years, the change in T1D incidence among immigrants from a low-risk country to a high-risk country and the difference in risk between children of an affected father (7% risk) and of an affected mother (3% risk) underscore the role of environmental factors in T1D . This explains the dilution of the frequency of high-risk HLA genes in the T1D population, such as the DR4-DQ8 or DR3-DQ2 genotypes in T1D children declined over the past 40 years. Environmental factors are thought to play a role both in the triggering and in the progression of islet autoimmunity. In children with close genetic susceptibility, the incidence of overt T1D increased without an increase in the incidence of prediabetes.

Many hypothetical models may contribute to explaining how the environment triggers T1D. The hygiene hypothesis postulates that decreasing childhood infections linked to a better hygiene impairs the development of the immune system, limits the competition between self and non-self and disturbs T-cell regulation.

The accelerator hypothesis – β cell stress hypothesis – postulates that insulin resistance secondary to accelerated growth or rapid weight gain triggers endoplasmic reticulum stress in β cells and possibly autoimmunity The fertile field hypothesis suggests that infections would make the body more prone to develop autoimmunity by favoring responses to autoantigen. The "old friends' hypothesis" implies that the lack of exposure to normal microbiota impairs immune system regulation and maturation. Finally, the threshold hypothesis, which calculates and quantify the contribution of each genetic and environmental factor, suggests that an accumulation of events induces enough stimulation to overcome T-cell activation thresholds and trigger immune responses.

Many studies were conducted to study the influence of environmental factors on the development of islet autoimmunity and T1D in children. TEDDY has already evaluated candidate environmental triggers, including infections, probiotics, micronutrients, and microbiota. Potential factors influencing the risk of T1D have been identified. For many of these factors, the evidence is low and often controversial.

Economic Burden:

The cost of diabetes management and its complications poses a significant economic burden on individuals and healthcare systems. Identifying trends can help allocate resources more effectively. The total estimated cost of diagnosed diabetes in the U.S. in 2022 is $412.9 billion, including $306.6 billion in direct medical costs and $106.3 billion in indirect costs attributable to diabetes. For cost categories analyzed, care for people diagnosed with diabetes accounts for 1 in 4 health care dollars in the U.S., 61% of which are attributable to diabetes.

On average people with diabetes incur annual medical expenditures of $19,736, of which approximately $12,022 is attributable to diabetes. People diagnosed with diabetes, on average, have medical expenditures 2.6 times higher than what would be expected without diabetes. Glucose-lowering medications and diabetes supplies account for ∼17% of the total direct medical costs attributable to diabetes.

Major contributors to indirect costs are reduced employment due to disability ($28.3 billion), presenteeism ($35.8 billion), and lost productivity due to 338,526 premature deaths ($32.4 billion). The inflation-adjusted direct medical costs of diabetes are estimated to rise 7% from 2017 and 35% from 2012 calculations (stated in 2022 dollars).

Following decades of steadily increasing prevalence of diabetes, the overall estimated prevalence in 2022 remains relatively stable in comparison to 2017. However, the absolute number of people with diabetes has grown and contributes to increased health care expenditures, particularly per capita spending on inpatient hospital stays and prescription medications. The enormous economic toll of diabetes continues to burden society through direct medical and indirect costs. Diabetes poses a substantial burden on society in the form of higher direct medical costs, lost productivity, premature mortality, and intangible costs in the form of reduced social connectivity and quality of life.

The estimated economic burden of diabetes in 2017 was $327 billion in 2017 USD, including $237 billion in direct medical costs and $90 billion in reduced productivity. Furthermore, more than half of the total expenditure was directly attributable to diabetes and its complications.

According to the Centers for Disease Control and Prevention (CDC), the prevalence of diagnosed diabetes among adults between 2017 and 2021 has remained relatively stable in the U.S. at 8.5%. Nevertheless, shifts in demographics of the population with diabetes and changes in health care delivery, therapies, and technology affect the economic burden associated with diabetes.

These factors all play a role in determining the burden of diabetes at a given point in time. In response to the health and economic impacts of diabetes, a variety of prevention programs and interventions have been introduced in the past decade, encompassing new care delivery models, policy measures, and community-based diabetes prevention lifestyle interventions, as well as therapeutic innovation such as incretin hormone receptor agonists, including glucagon-like peptide 1 and glucose-dependent insulinotropic polypeptide.

Diabetes- Trends and Updates Exam

1. **What hormone is primarily responsible for regulating blood sugar levels?**
    - A) Glucagon
    - B) Insulin
    - C) Adrenaline
    - D) Cortisol
2. **Which type of diabetes is characterized by the body's inability to produce insulin?**
    - A) Type 1 Diabetes
    - B) Type 2 Diabetes
    - C) Gestational Diabetes
    - D) MODY Diabetes
3. **Type 2 diabetes is also known as:**
    - A) Juvenile diabetes
    - B) Insulin-dependent diabetes
    - C) Non-insulin-dependent diabetes
    - D) Gestational diabetes
4. **What is the main difference between Type 1 and Type 2 diabetes?**
    - A) Age of onset
    - B) Cause of high blood sugar
    - C) Treatment methods
    - D) All of the above
5. **Which type of diabetes often occurs during pregnancy?**
    - A) Type 1 Diabetes
    - B) Type 2 Diabetes
    - C) Gestational Diabetes
    - D) MODY Diabetes

6. **Which region has the highest prevalence of diabetes according to the IDF Diabetes Atlas?**
    - A) North America
    - B) Middle East and North Africa
    - C) South America
    - D) Europe

7. **Which of the following is a modifiable risk factor for Type 2 diabetes?**
    - A) Genetic predisposition
    - B) Age
    - C) Physical inactivity
    - D) Family history
8. **What socioeconomic factor is positively associated with diabetes prevalence?**
    - A) High alcohol consumption
    - B) High tobacco consumption
    - C) High levels of physical activity
    - D) Low unemployment rates
9. **Obesity is a significant risk factor for:**
    - A) Type 1 Diabetes
    - B) Type 2 Diabetes
    - C) Gestational Diabetes
    - D) All types of diabetes
10. **The term "diabetes mellitus" refers to:**
    - A) The sweet taste of glucose in urine
    - B) A deficiency in glucose metabolism
    - C) Insulin resistance
    - D) Increased blood glucose levels

11. **Which diagnostic test measures long-term blood sugar control?**
    - A) Fasting glucose test
    - B) Oral glucose tolerance test
    - C) HbA1c test
    - D) Insulin tolerance test
12. **What is the recommended HbA1c level for most adults with diabetes?**
    - A) Less than 6.0%
    - B) Less than 6.5%
    - C) Less than 7.0%
    - D) Less than 7.5%

13. **The primary treatment for Type 1 diabetes involves:**
    - A) Oral medications
    - B) Diet and exercise
    - C) Insulin injections
    - D) Weight loss surgery
14. **Which of the following is an emerging technology in diabetes management?**
    - A) Insulin pumps
    - B) Continuous glucose monitors
    - C) Glucose tablets
    - D) Diet-based therapy
15. **What role do genetics play in the development of Type 2 diabetes?**
    - A) They are the sole factor
    - B) They interact with environmental and lifestyle factors
    - C) They have no significant role
    - D) They are more important than lifestyle factors

16. **According to recent studies, what percentage of global adults were estimated to have diabetes in 2019?**
    - A) 4.7%
    - B) 8.5%
    - C) 9.3%
    - D) 10.9%
17. **Which lifestyle factor is associated with a lower prevalence of diabetes?**
    - A) High-fat diet
    - B) High alcohol consumption
    - C) Regular physical activity
    - D) High sugar intake
18. **Urbanization is linked to increased diabetes prevalence due to:**
    - A) Increased physical activity
    - B) Reduced access to healthcare
    - C) Changes in dietary patterns
    - D) Lower socioeconomic status

19. **What is the primary goal of diabetes management?**
    - A) Eliminate insulin use
    - B) Prevent all diabetes-related complications
    - C) Maintain blood glucose levels within target ranges
    - D) Achieve weight loss
20. **Which organization provides comprehensive data on global diabetes trends?**
    - A) World Health Organization (WHO)
    - B) International Diabetes Federation (IDF)
    - C) National Institutes of Health (NIH)
    - D) Centers for Disease Control and Prevention (CDC)

21. **Recent advances in diabetes research include:**
    - A) New forms of insulin
    - B) Genetic studies linking specific genes to diabetes risk
    - C) Improved dietary guidelines
    - D) All of the above
22. **What is the significance of understanding diabetes trends?**
    - A) It helps in developing treatments
    - B) It aids in prevention strategies
    - C) It provides insight into public health impacts
    - D) All of the above
23. **Which population has shown a growing prevalence of diabetes in recent years?**
    - A) Children and adolescents
    - B) Older adults
    - C) Rural communities
    - D) Urban populations
24. **Diabetes-related complications are most effectively prevented through:**
    - A) Early detection and management
    - B) Use of advanced medications
    - C) Avoidance of physical activity
    - D) Restrictive diets
25. **Which statement best describes the future outlook of diabetes prevalence?**
    - A) It is expected to decline
    - B) It will likely remain stable
    - C) It is projected to increase
    - D) It is unpredictable

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