Diabetes Mellitus (DM) – Part 1

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(Lecture for Week 5 for Publishing in SPU Website)

Diabetes Mellitus (DM)

- It is a syndrome with disordered metabolism and inappropriate hyperglycemia due to
  - either a deficiency of insulin secretion,
  - or a combination of insulin resistance and inadequate insulin secretion to compensate for the resistance

DM: Epidemiologic Considerations

Per CMDT 2020: An estimated 30.3 million people (9.4%) in the United States have diabetes mellitus,

- of which approximately 1.5 million have type 1 diabetes
- and most of the rest have type 2 diabetes
- A third group designated as "specific types of diabetes due to other causes" by the American Diabetes Association (ADA) number in the thousands

DM: Classification & Pathogenesis

A) Type 1 Diabetes Mellitus

- It results from pancreatic islet β-cell destruction
  - predominantly by a cellular-mediated autoimmune process in over 95% of cases (type 1A)
  - and idiopathic in less than 5% (type 1B)

DM: Classification & Pathogenesis

A) Type 1 Diabetes Mellitus

- It can be a catabolic disorder in which circulating insulin is virtually absent, plasma glucagon is elevated, pancreatic β cells fail to respond to all insulinogenic stimuli, and ketosis is usually associated in its untreated state

20.1 Metabolic actions of insulin

Increase	Decrease
Carbohydrate metabolism	
Glucose transport (muscle, adipose tissue)	Gluconeogenesis
Glucose phosphorylation	Glycogenolysis
Glycogen synthesis	
Glycolysis	
Pyruvate dehydrogenase activity	
Pentose phosphate shunt	
Lipid metabolism	
Triglyceride synthesis	Lipolysis
Fatty acid synthesis (liver)	Lipoprotein lipase (muscle)
Lipoprotein lipase activity (adipose tissue)	Ketogenesis
	Fatty acid oxidation (liver)
Protein metabolism	
Amino acid transport	Protein degradation
Protein synthesis	

Davidson's Principles and Practice of Medicine, 23rd Edition; 2018; Chapter 20; Page 723

DM: Classification & Pathogenesis

A) Type 1 Diabetes Mellitus

- Therefore, exogenous insulin is required to reverse the catabolic state, prevent ketosis, and reduce the hyperglucagonemia and the hyperglycemia

DM: Classification & Pathogenesis

A) Type 1 Diabetes Mellitus

1. Immune-mediated diabetes (type 1A)

- Previously called "insulin-dependent diabetes" or "juvenile-onset diabetes"

DM: Classification & Pathogenesis

A) Type 1 Diabetes Mellitus

1. Immune-mediated diabetes (type 1A)

- Autoimmune markers include islet cell autoantibodies (ICA) and autoantibodies to glutamic acid decarboxylase 65 (GAD 65), insulin (IAA), tyrosine phosphatases IA-2 and IA-2β, and zinc transporter 8 (ZnT8)

DM: Classification & Pathogenesis

A) Type 1 Diabetes Mellitus

1. Immune-mediated diabetes (type 1A)

- Type 1A diabetes is defined by the presence of one or more of those autoimmune markers

- Note that low levels of anti-insulin antibodies develop in almost all patients once they are treated with insulin (then they cannot be diagnostic for type 1A diabetes)

DM: Classification & Pathogenesis

A) Type 1 Diabetes Mellitus

1. Immune-mediated diabetes (type 1A)

- Commonly occurs in children and young adults (peak incidence before school age and again at around puberty), but it can occur at any age, even in the 8th and 9th decades of life

DM: Classification & Pathogenesis

A) Type 1 Diabetes Mellitus

1. Immune-mediated diabetes (type 1A)

- The rate of pancreatic β cell destruction is variable, being rapid in some individuals (mainly infants and children) and slow in others (mainly adults)

DM: Classification & Pathogenesis

A) Type 1 Diabetes Mellitus

1. Immune-mediated diabetes (type 1A)

- Some patients with a milder expression of type 1 DM initially retain enough β cell function to avoid ketosis, but as their β cell mass diminishes later in life, dependence on insulin therapy develops

DM: Classification & Pathogenesis

A) Type 1 Diabetes Mellitus

1. Immune-mediated diabetes (type 1A)

- Islet cell antibody surveys among northern Europeans indicate that up to 15% of "type 2" diabetic patients may actually have that mild form of type 1 diabetes (latent autoimmune diabetes of adulthood "LADA")

DM: Classification & Pathogenesis

A) Type 1 Diabetes Mellitus

1. Immune-mediated diabetes (type 1A)

- Approximately one-third of the disease susceptibility is due to genes and two-thirds to environmental factors

DM: Classification & Pathogenesis

A) Type 1 Diabetes Mellitus

1. Immune-mediated diabetes (type 1A)
   - Genes that are related to the HLA locus contribute about 40% of the genetic risk
   - About 95% of patients with type 1 diabetes possess either HLA-DR3 or HLA-DR4, compared with 45-50% of white controls

DM: Classification & Pathogenesis

A) Type 1 Diabetes Mellitus

1. Immune-mediated diabetes (type 1A)

- HLA-DQ genes are even more specific markers of type 1 susceptibility, since a particular variety (HLA-DQB1*0302) is found in the DR4 patients with type 1, while a "protective" gene (HLA-DQB1*0602) is often present in the DR4 controls

DM: Classification & Pathogenesis

A) Type 1 Diabetes Mellitus

1. Immune-mediated diabetes (type 1A)

- However, most individuals with predisposing haplotypes do not develop diabetes

DM: Classification & Pathogenesis

A) Type 1 Diabetes Mellitus

1. Immune-mediated diabetes (type 1A)

- The other important gene that contributes to about 10% of the genetic risk is found at the 5' polymorphic region of the insulin gene

DM: Classification & Pathogenesis

A) Type 1 Diabetes Mellitus

1. Immune-mediated diabetes (type 1A)

- Mutations in genes associated with T cell tolerance can also cause autoimmune diabetes
- The autoimmune regulatory (AIRE) gene product regulates the expression of several proteins in the thymus causing the deletion of self-reactive T cells

DM: Classification & Pathogenesis

A) Type 1 Diabetes Mellitus

1. Immune-mediated diabetes (type 1A)

- Type 1 diabetes mellitus as well as other autoimmune disorders (autoimmune polyglandular syndrome 1 "APS-1") can develop in individuals with homozygous mutations in the AIRE gene

DM: Classification & Pathogenesis

A) Type 1 Diabetes Mellitus

1. Immune-mediated diabetes (type 1A)

- There are other identified genetic loci that contribute susceptibility to type 1 DM (i.e., polygenic susceptibility)

DM: Classification & Pathogenesis

A) Type 1 Diabetes Mellitus

1. Immune-mediated diabetes (type 1A)

- Although the risk of developing type 1 DM is increased tenfold in relatives of individuals with the disease, the risk is relatively low:

DM: Classification & Pathogenesis

20.6 Risk of type 1 diabetes among first-degree relatives of patients with type 1 diabetes

Relative with type 1 diabetes	% overall risk
Identical twin	30–50
Non-identical twin	6–10
HLA-identical sibling	16
Non-HLA-identical sibling	5
Father	10
Mother	1–4
Both parents	Up to 30

DM: Classification & Pathogenesis

A) Type 1 Diabetes Mellitus

1. Immune-mediated diabetes (type 1A)

- Hence, most individuals with newly diagnosed type 1 DM (80-85 %) do not have a first-degree relative with this disorder

DM: Classification & Pathogenesis

A) Type 1 Diabetes Mellitus

1. Immune-mediated diabetes (type 1A)

- Evidence for environmental factors playing a role in the development of type 1 diabetes include the observation that the disease is more common in Scandinavian countries and becomes progressively less frequent in countries nearer and nearer to the equator

DM: Classification & Pathogenesis

A) Type 1 Diabetes Mellitus

1. Immune-mediated diabetes (type 1A)

- Also, the risk for type 1 diabetes increases when individuals who normally have a low risk emigrate to the Northern Hemisphere

DM: Classification & Pathogenesis

A) Type 1 Diabetes Mellitus

1. Immune-mediated diabetes (type 1A)

- For example, Pakistani children born and raised in Bradford, England, have a higher risk for developing type 1 diabetes compared with children who lived in Pakistan all their lives

DM: Classification & Pathogenesis

A) Type 1 Diabetes Mellitus

1. Immune-mediated diabetes (type 1A)

- Which environmental factor is responsible for the increased risk is not known

DM: Classification & Pathogenesis

A) Type 1 Diabetes Mellitus

1. Immune-mediated diabetes (type 1A)

- Numerous environmental factors have been proposed to trigger the autoimmune process in genetically susceptible individuals; however, none have been conclusively linked to diabetes

DM: Classification & Pathogenesis

A) Type 1 Diabetes Mellitus

1. Immune-mediated diabetes (type 1A)

- Identification of an environmental trigger has been difficult because the event may precede the onset of DM by several years

DM: Classification & Pathogenesis

A) Type 1 Diabetes Mellitus

1. Immune-mediated diabetes (type 1A)

- Putative environmental triggers include viruses (coxsackie, rubella, enteroviruses most prominently), bovine milk proteins, nitrosourea compounds, vitamin D deficiency, and environmental toxins
- Breastfeeding in the first 6 months of life appears to be protective

DM: Classification & Pathogenesis

A) Type 1 Diabetes Mellitus

1. Immune-mediated diabetes (type 1A)

- There is accumulating evidence that improvements in public health and reduced infections (esp. parasitic) lead to immune system dysregulation and development of autoimmune disorders such as type 1 diabetes (microbiota / hygiene hypothesis)

DM: Classification & Pathogenesis

A) Type 1 Diabetes Mellitus

1. Immune-mediated diabetes (type 1A)

- Check point inhibitor immunotherapies for advanced malignancies, such as nivolumab, pembrolizumab, and ipilimumab, can precipitate autoimmune disorders, including type 1 diabetes

DM: Classification & Pathogenesis

A) Type 1 Diabetes Mellitus

1. Immune-mediated diabetes (type 1A)

   => Therefore, patients receiving those drugs should be monitored for the development of diabetes

DM: Classification & Pathogenesis

A) Type 1 Diabetes Mellitus

- It is due to pancreatic islet B cell destruction
  - predominantly by an **autoimmune** process in over 95% of cases **(type 1A)**
  - **and idiopathic in less than 5% (type 1B)**

DM: Classification & Pathogenesis

A) Type 1 Diabetes Mellitus

2. Idiopathic type 1 diabetes (type 1B)

- These patients have insulinopenia and get ketoacidosis but do not have evidence of pancreatic β-cell autoimmunity to explain those findings

DM: Classification & Pathogenesis

A) Type 1 Diabetes Mellitus

2. Idiopathic type 1 diabetes (type 1B)

- Although only a minority of patients with type 1 diabetes fall into this group, most of these individuals are of Asian or African origin

DM: Classification & Pathogenesis

A) Type 1 Diabetes Mellitus

2. Idiopathic type 1 diabetes (type 1B)

- Patients suffer from episodic DKA (ketosis-prone) and exhibit varying degrees of insulin deficiency between episodes

DM: Classification & Pathogenesis

A) Type 1 Diabetes Mellitus

2. Idiopathic type 1 diabetes (type 1B)

- It is strongly inherited and is not HLA associated

- An absolute requirement for insulin replacement therapy may be intermittent

DM: Epidemiologic Considerations

- Per CMDT 2019: An estimated 30.3 million people (9.4%) in the United States have diabetes mellitus,
  - of which approximately 1.5 million have **type 1 diabetes**
  - and most of the rest have **type 2 diabetes**
  - A third group designated as **"specific types of diabetes due to other causes"** by the American Diabetes Association (ADA) number in the thousands

DM: Classification & Pathogenesis

B) Type 2 Diabetes Mellitus

- Previously referred to as "noninsulin-dependent diabetes" or "adult-onset diabetes"

- It is a diagnosis of exclusion, i.e. it is made when type 1 diabetes and other types of diabetes are ruled out

DM: Classification & Pathogenesis

B) Type 2 Diabetes Mellitus

- It used to occur predominantly in adults, but it is now more frequently encountered in children and adolescents

DM: Classification & Pathogenesis

B) Type 2 Diabetes Mellitus

- It is a state of relative (rather than absolute) insulin deficiency in which circulating endogenous insulin is sufficient to prevent ketoacidosis but is inadequate to prevent hyperglycemia in the face of increased needs owing to tissue insensitivity (i.e., insulin resistance)

DM: Classification & Pathogenesis

B) Type 2 Diabetes Mellitus

- Excessive or inappropriate glucagon secretion contributes to the pathophysiology

DM: Classification & Pathogenesis

B) Type 2 Diabetes Mellitus

- Early in the disease process, hyperplasia of pancreatic β-cells occurs and probably accounts for the fasting hyperinsulinism and exaggerated insulin and proinsulin responses to glucose and other stimuli

DM: Classification & Pathogenesis

B) Type 2 Diabetes Mellitus

- With time, chronic deposition of amyloid in the islets may combine with inherited genetic defects to impair β-cell function progressively

DM: Classification & Pathogenesis

B) Type 2 Diabetes Mellitus

- Genetic and environmental factors combine to cause both the insulin resistance and the β-cell loss

DM: Classification & Pathogenesis

B) Type 2 Diabetes Mellitus

- The genetic influence is strong as shown by marked differences in susceptibility in different ethnic groups *and* by studies in monozygotic twins where concordance rates approach 100%

DM: Classification & Pathogenesis

B) Type 2 Diabetes Mellitus

- So far, more than 30 genetic loci have been associated with an increased risk of type 2 diabetes

- A significant number of the identified loci appear to code for proteins that have a role in β-cell function or development

DM: Classification & Pathogenesis

B) Type 2 Diabetes Mellitus

- ***Obesity*** is the most important **environmental** factor causing insulin resistance

- The degree and prevalence of *obesity* varies among different racial groups with type 2 diabetes

DM: Classification & Pathogenesis

B) Type 2 Diabetes Mellitus

- While obesity is apparent in no more than 30% of Chinese and Japanese patients with type 2, it is found in 60-70% of North Americans, Europeans, or Africans with type 2 and approaches 100% of patients with type 2 among Pima Indians or Pacific Islanders from Nauru or Samoa

DM: Classification & Pathogenesis

B) Type 2 Diabetes Mellitus

- Visceral obesity, due to accumulation of fat in the omental and mesenteric regions, correlates with insulin resistance

- Subcutaneous abdominal fat seems to have less of an association with insulin insensitivity

DM: Classification & Pathogenesis

B) Type 2 Diabetes Mellitus

- There are many patients with type 2 diabetes who, while not overtly obese, have increased visceral fat => they are termed the "metabolically obese"

DM: Classification & Pathogenesis

B) Type 2 Diabetes Mellitus

- *Exercise* may affect the deposition of visceral fat as suggested by CT scans of Japanese wrestlers, whose extreme obesity is predominantly subcutaneous as their daily vigorous exercise program prevents accumulation of visceral fat, and they have normal serum lipids and euglycemia despite daily intakes of 5000–7000 kcal and development of massive subcutaneous obesity

Sumo Wrestler Asashōryū fighting against Kotoshogiku at the January Tournament 2008 By Eckhard Pecher User:Arcimboldo - Own work, CC BY 3.0, https://commons.wikimedia.org/w/index.php?curid=3381800

DM: Classification & Pathogenesis

B) Type 2 Diabetes Mellitus

- So physical activity is another important determinant of insulin sensitivity

- Sedentary people are more insulin-resistant than active people with the same degree of obesity

DM: Classification & Pathogenesis

B) Type 2 Diabetes Mellitus

- Moreover, physical activity allows non-insulin-dependent glucose uptake into muscle, reducing the 'demand' on the pancreatic β-cells to produce insulin

DM: Classification & Pathogenesis

B) Type 2 Diabetes Mellitus

- Type 2 diabetes and its prediabetes antecedents belong to a cluster of conditions thought to be caused by resistance to insulin action and the ensuing hyperinsulinemia (however, supportive evidence is inconclusive)

DM: Classification & Pathogenesis

B) Type 2 Diabetes Mellitus

- Thus, people with type 2 diabetes or prediabetes often have associated disorders including:
  - Hypertension
  - Dyslipidemia (characterized by elevated levels of small dense LDL cholesterol and triglycerides, and a low level of HDL cholesterol)
  - Polycystic ovarian syndrome (PCOS)

DM: Classification & Pathogenesis

B) Type 2 Diabetes Mellitus

- Non-alcoholic fatty liver disease (NAFLD)
- Abdominal obesity (waistline ≥ 88 cm for women and ≥ 102 cm for men)
- Hyperuricemia
- Prothrombotic state with increased levels of plasminogen activator inhibitor type 1 (PAI-1)

DM: Classification & Pathogenesis

B) Type 2 Diabetes Mellitus

- Proinflammatory state with increased levels of proinflammatory cytokines such as IL-6 and TNF-alpha

- This cluster has been termed the 'insulin resistance syndrome' or 'metabolic syndrome'

DM: Classification & Pathogenesis

B) Type 2 Diabetes Mellitus

- The main value of grouping these disorders as a syndrome is to remind clinicians that the therapeutic goals are not only to correct hyperglycemia but also to manage the elevated blood pressure and dyslipidemia that result in increased cerebrovascular and cardiac morbidity and mortality in these patients

DM: Epidemiologic Considerations

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DM: Classification & Pathogenesis

C) Specific types of diabetes due to other causes

1) **Diseases of the exocrine pancreas (e.g., pancreatitis, cystic fibrosis, hemochromatosis, pancreatectomy, neoplastic disease) [due to reduced insulin secretion]**

DM: Classification & Pathogenesis

C) Specific types of diabetes due to other causes

2) Endocrinopathies

- Acromegaly, Cushing syndrome, glucagonoma, thyrotoxicosis, pheochromocytoma (due to tissue insensitivity to insulin)
- Somatostatinoma, pheochromocytoma (due to reduced insulin secretion)

DM: Classification & Pathogenesis

C) Specific types of diabetes due to other causes

3) Drug- or chemical-induced diabetes

- due to tissue insensitivity to insulin (such as corticosteroids, sympathomimetics)
- due to reduced insulin secretion (such as thiazide diuretics, phenytoin, cyclosporine)

DM: Classification & Pathogenesis

C) Specific types of diabetes due to other causes

4) Monogenic diabetes

a) Genetic defects of *insulin action* (such as lipodystrophies)

DM: Classification & Pathogenesis

C) Specific types of diabetes due to other causes

4) Monogenic diabetes

b) Genetic defects of *β-cell development or function* - most common, and they cause two diabetes subtypes among others:

i. Maturity-onset diabetes of the young (MODY)

ii. Neonatal diabetes

DM: Classification & Pathogenesis

C) Specific types of diabetes due to other causes 4) Monogenic diabetes

- Maturity-onset diabetes of the young (MODY) Six types have been described (MODY 1 through MODY 6), and this subgroup is characterized by:
  - ✓ Autosomal dominant inheritance
  - ✓ An age at onset of 25 years or younger
  - ✓ patients being nonobese

DM: Classification & Pathogenesis

C) Specific types of diabetes due to other causes 4) Monogenic diabetes

- ❖ Maturity-onset diabetes of the young (MODY)
  - ✓ Noninsulin requiring diabetes
  - ✓ The hyperglycemia is due to impaired glucose-induced secretion of insulin

DM: Classification & Pathogenesis

C) Specific types of diabetes due to other causes 4) Monogenic diabetes

- Neonatal (or Congenital) diabetes
  - ✓ Occurs under 6 months of age, and much less often after 6 months of age, whereas autoimmune type 1 diabetes rarely occurs before 6 months of age
  - ✓ It can either be transient or permanent

DM: Classification & Pathogenesis

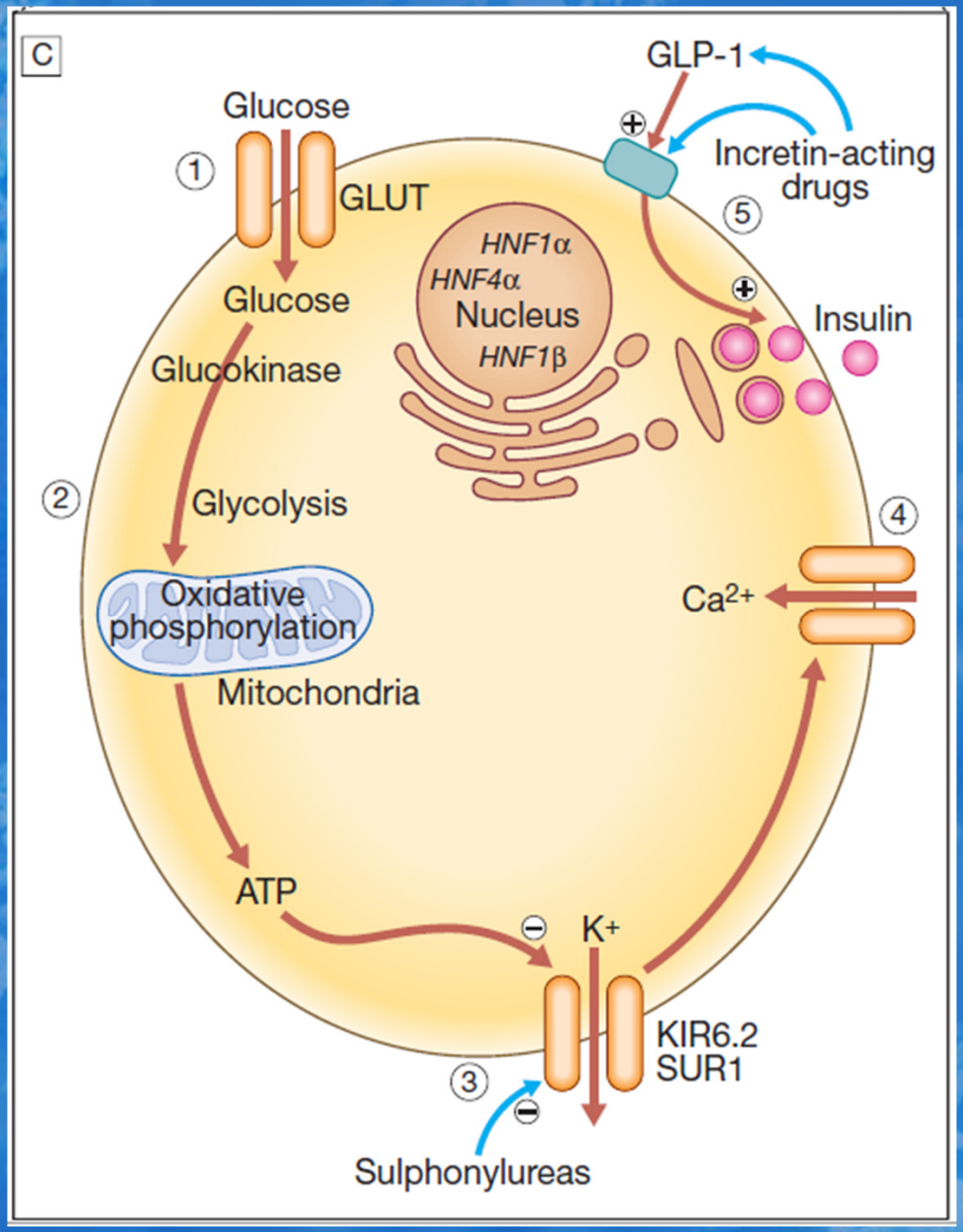
C) Specific types of diabetes due to other causes 4) Monogenic diabetes

- Neonatal (or Congenital) diabetes
  - ✓ About 80-85% of cases can be found to have an underlying monogenic cause
  - ✓ The presentation is usually that of profound insulin deficiency with marked hyperglycemia and DKA

DM: Classification & Pathogenesis

C) Specific types of diabetes due to other causes 4) Monogenic diabetes

- Neonatal (or Congenital) diabetes
  - ✓ Permanent neonatal diabetes is most commonly due to autosomal dominant activating mutations in the genes encoding the Kir6.2 and SUR1 subunits of the β-cell K_{ATP} channel



Davidson's Principles and Practice of Medicine, 23rd Edition; 2018; Chapter 20; Page 723

DM: Classification & Pathogenesis

C) Specific types of diabetes due to other causes 4) Monogenic diabetes

- Neonatal (or Congenital) diabetes
  - ✓ Correct diagnosis has critical implications because most patients with K_{ATP}-related neonatal diabetes will exhibit improved glycemic control when treated with high-dose oral sulfonylureas instead of insulin

DM: Classification & Pathogenesis

C) Specific types of diabetes due to other causes

5) **Associated with genetic syndromes**

(e.g. Klinefelter syndrome, Turner syndrome, DIDMOAD "Wolfram syndrome", Down syndrome)

DM: Classification & Pathogenesis

C) Specific types of diabetes due to other causes

6) **Uncommon forms of immune-mediated diabetes** (e.g. anti-insulin receptor antibodies)

DM: Epidemiologic Considerations

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DM: Classification & Pathogenesis

- **Of note:** The American Diabetes Association (ADA) has, in addition to the three categories of classification for diabetes (type 1, type 2, and specific types due to other causes), **a 4th category called …**

DM: Classification & Pathogenesis

- … Gestational diabetes mellitus (GDM) => it is diabetes diagnosed in the second or third trimester of pregnancy that was not clearly overt diabetes prior to gestation

[GDM shall not be covered in this course as it should be covered in the Obstetrics course]

DM: Symptoms & Signs