Diabetes Mellitus (DM) – Part 2

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(Lecture for Week 6 for Publishing in SPU Website)

DM: Symptoms & Signs

DM: Symptoms & Signs

1) Type 1 Diabetes:

DM: Symptoms & Signs

1) Type 1 Diabetes:

- The classic symptoms of type 1 diabetes are:
  - Polyuria
  - Polydipsia
  - Polyphagia
  - Unexplained weight loss

- Other symptoms may include fatigue, weakness, nausea, and blurred vision

DM: Symptoms & Signs

1) Type 1 Diabetes:

- Loss of subcutaneous fat and muscle wasting can be seen (features of more slowly developing insulin deficiency)

- Note that although patients are not typically obese when they present with type 1 diabetes, obesity should not preclude the diagnosis

DM: Symptoms & Signs

1) Type 1 Diabetes:

- Paresthesias may be present at the time of diagnosis, particularly when the onset is subacute ~ they reflect a temporary dysfunction of peripheral sensory nerves, which clears as insulin replacement restores glycemic levels closer to normal, suggesting neurotoxicity from sustained hyperglycemia

DM: Symptoms & Signs

1) Type 1 Diabetes:

- Symptoms and signs of postural hypotension may occur, and hypotension in the recumbent position is a serious prognostic sign

DM: Symptoms & Signs

1) Type 1 Diabetes:

- The onset of symptomatic disease may be sudden ~ it is not unusual for patients with type 1 diabetes to present with diabetic ketoacidosis (DKA)

DM: Symptoms & Signs

1) Type 1 Diabetes:

- A "honeymoon" period, marked by restoration of euglycemia, may occur soon after disease onset

- However, the duration of this phase is highly variable, and all patients eventually require insulin

DM: Symptoms & Signs

1) Type 1 Diabetes:

- People with type 1 diabetes are also prone to other autoimmune disorders such as Hashimoto thyroiditis, Graves disease, Addison disease, celiac disease, vitiligo, autoimmune hepatitis, myasthenia gravis, and pernicious anemia

DM: Symptoms & Signs

2) Type 2 Diabetes:

DM: Symptoms & Signs

2) Type 2 Diabetes:

- Many patients have an insidious onset of hyperglycemia and are asymptomatic initially (this is particularly true in obese patients, whose diabetes may be detected only after glycosuria or hyperglycemia is noted during routine laboratory studies)

DM: Symptoms & Signs

2) Type 2 Diabetes:

- Some patients may present with symptoms of increased urination and thirst (polyuria and polydipsia, respectively)

- Occasionally, when the disease has been occult for some time, patients may have symptoms and/or signs of diabetes complications (e.g. neuropathy, MI, PAD) at the time of presentation

DM: Symptoms & Signs

2) Type 2 Diabetes:

- Blurred vision may be present
- Chronic skin infections are common
- Generalized pruritus may occur (due to xerosis, neuropathy, ischemia, cytokines, drugs, skin products, and/or ESRD)
- Symptoms of vaginitis are frequently the initial complaints of women

DM: Symptoms & Signs

2) Type 2 Diabetes:

- Diabetes should be suspected in women with chronic candidal vulvovaginitis as well as in those who have delivered babies larger than 9 lb (4.1 kg) or have had polyhydramnios, preeclampsia, or unexplained fetal losses

- Balanoposthitis (inflammation of the foreskin and glans in uncircumcised males) may occur

DM: Symptoms & Signs

2) Type 2 Diabetes:

- Many patients with type 2 diabetes are overweight or obese

- Even those who are not significantly obese often have characteristic centripetal localization of fat deposits (particularly the abdomen, chest, neck, and face) and relatively less fat on the appendages, which may be quite muscular

DM: Symptoms & Signs

2) Type 2 Diabetes:

- The centripetal fat distribution is characterized by a high waist circumference (≥102 cm in men and ≥88 cm in women)

DM: Symptoms & Signs

2) Type 2 Diabetes:

- Some patients may have acanthosis nigricans (the skin in the axilla, groin, and back of neck is hyperpigmented and hyperkeratotic ~ dark velvety appearance) which is associated with significant insulin resistance

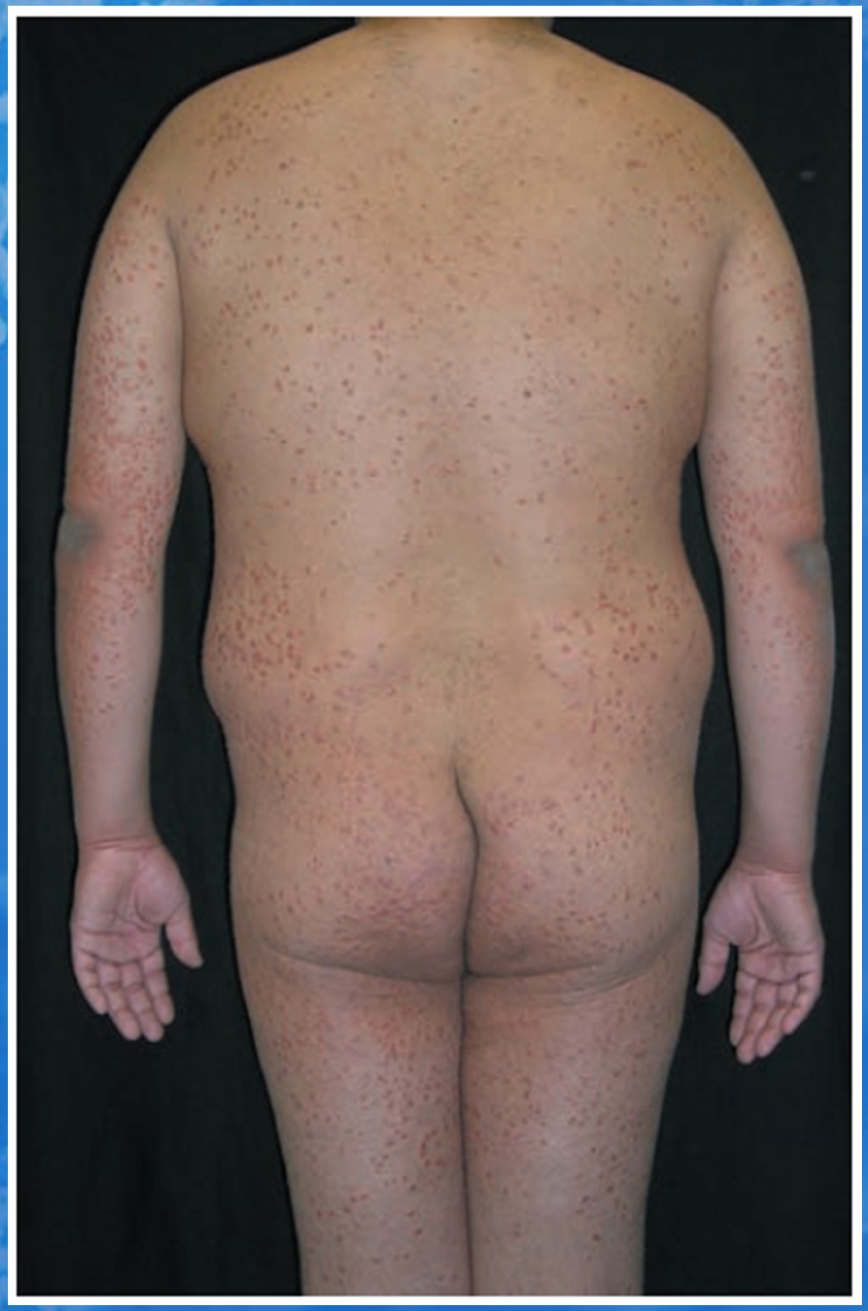
Current Medical Diagnosis and Treatment 2019, Page 1224 [Figure 27–1. Acanthosis nigricans of the nape of the neck, with typical dark and velvety appearance. (Used, with permission, from Umesh Masharani, MB, BS, MRCP [UK].)]

DM: Symptoms & Signs

2) Type 2 Diabetes:

- Mild hypertension is often present in obese patients with diabetes

- Eruptive xanthomas on the extensor surface of the limbs and on the buttocks and lipemia retinalis due to hyperchylomicronemia can occur in patients with uncontrolled type 2 diabetes who also have a familial form of hypertriglyceridemia



Usatine RP, Smith MA, Mayeaux EJ Jr, Chumley HS, eds; The Color Atlas of Family Medicine; Second Edition; McGraw-Hill Education; 2013; Page 1323 [FIGURE 223-3 (Courtesy of Richard P. Usatine, MD.)] Eruptive xanthomas covering most of the body of a 27-year-old man with untreated hyperlipidemia and diabetes.

DM: Symptoms & Signs

2) Type 2 Diabetes:

- Symptoms and/or signs of the other disorders associated with insulin resistance can be present (e.g. hepatomegaly, hirsutism, menstrual irregularities)

DM: Symptoms & Signs

2) Type 2 Diabetes:

- A hyperglycemic hyperosmolar state (HHS) can be present (in these cases, patients are profoundly dehydrated, hypotensive, lethargic or comatose but without the Kussmaul respirations that could be seen in DKA)

[Kussmaul respirations ~ deep, sighing breaths ~ acidotic breathing]

DM: Diagnosis

DM: Diagnosis

- Diabetes may be diagnosed based on
  - ***Either*** the plasma glucose criteria
    - ✓ the fasting plasma glucose (**FPG**)
    - ✓ or the 2-h plasma glucose (**2-h PG**) value with the 75-g oral glucose tolerance test (OGTT)
    - ✓ or the random plasma glucose
  - ***Or*** the Hemoglobin A_{1c} (**A1C**) criteria
- The tests do not necessarily detect diabetes in the same individuals

DM: Diagnosis

[Hemoglobin A_{1c} (A1C) is produced by nonenzymatic condensation of glucose molecules with free amino groups on the globin component of hemoglobin]

DM: Diagnosis

- The diagnostic cut points for diabetes are:
  - An **FPG** level of ≥126 mg/dL after at least 8 hours of fasting (no caloric intake)
  - **2-h PG** ≥200 mg/dL during OGTT
  - **A1C** ≥6.5%
  - In a patient with classic symptoms of hyperglycemia or hyperglycemic crisis, a **random plasma glucose** ≥200 mg/dL

DM: Diagnosis

- The concordance between the FPG and 2-h PG tests is imperfect, as is the concordance between A1C and either glucose-based test

- Compared with FPG and A1C cut points, the 2-h PG value diagnoses more people with diabetes and prediabetes

DM: Diagnosis

The plasma or serum glucose

- Elevated capillary blood glucose/ fingerstick glucose levels raise the possibility of diabetes but are insufficient for diagnosis

DM: Diagnosis

The plasma or serum glucose

- The glucose concentration is 10-15% higher in plasma or serum than in whole blood because structural components of blood cells are absent

DM: Diagnosis

The oral glucose tolerance test (OGTT)

- A minimum of 150-200 g of carbohydrate per day should be included in the diet for 3 days preceding the test
- The patient should eat nothing after midnight prior to the test day
- On the morning of the test, patients are then given 75 g of glucose in 300 mL of water
- The glucose load is consumed within 5 minutes

DM: Diagnosis

The oral glucose tolerance test (OGTT)

- The test should be performed in the morning because there is some diurnal variation in oral glucose tolerance
- Patients should not smoke or be active during the test
- Blood samples for plasma glucose are obtained at 0 and 120 minutes after ingestion of glucose

DM: Diagnosis

The Hemoglobin A_{1c} (A1C) test

- To avoid misdiagnosis or missed diagnosis of diabetes, the A1C test should be performed using a method that is certified by the National Glycohemoglobin Standardization Program (NGSP) and standardized to the Diabetes Control and Complications Trial (DCCT) assay (this is done in the USA)

DM: Diagnosis

The Hemoglobin A_{1c} (A1C) test

- In the EU, the testing is standardized to the International Federation of Clinical Chemistry (IFCC)

DM: Diagnosis

The Hemoglobin A_{1c} (A1C) test

- The cutoff value of 6.5% was chosen because the risk for retinopathy increases substantially above this value

- The advantages of using the HbA1c to diagnose diabetes are:
  - no requirement for fasting or timed samples (greater convenience)

  - … =>

DM: Diagnosis

The Hemoglobin A_{1c} (A1C) test

- it has lower intraindividual variability than the fasting glucose test and the OGTT

- since HbA_{1c} circulates within red blood cells whose life span lasts up to 120 days, it generally reflects the state of glycemia over the preceding 8-12 weeks (providing an assessment of glucose control for the period as well)

DM: Diagnosis

The Hemoglobin A_{1c} (A1C) test

- A study reported that the relationship between average glucose in the previous 3 months and A1C was

  $(28.7 \times HbA_{1c}) - 46.7$ {ex.: if 8 => 183}

DM: Diagnosis

The Hemoglobin A_{1c} (A1C) test

- A study reported that the relationship between average glucose in the previous 3 months and A1C was

  $(28.7 \times HbA_{1c}) - 46.7$ {ex.: if 8 => 183}

- ***However,*** there is substantial individual variability and therefore caution should be exercised in estimating average glucose levels from measured HbA_{1c}

DM: Diagnosis

The Hemoglobin A_{1c} (A1C) test

- The accuracy of HbA_{1c} values can be affected by hemoglobin variants or traits
- In patients with high levels of hemoglobin F, immunoassays give falsely low values of HbA_{1c}

DM: Diagnosis

The Hemoglobin A_{1c} (A1C) test

- Any condition that shortens erythrocyte survival or decreases mean erythrocyte age or increases red cell turnover will falsely lower HbA_{1c}
- So hemolytic anemia, recent blood loss, transfusion, hemodialysis, pregnancy (2^{nd} and 3^{rd} trimesters), or erythropoietin therapy will falsely lower HbA1C levels

DM: Diagnosis

The Hemoglobin A_{1c} (A1C) test

- Vitamins C and E are reported to falsely lower test results possibly by inhibiting glycation of hemoglobin

DM: Diagnosis

The Hemoglobin A_{1c} (A1C) test

- Conditions that increase erythrocyte survival (such as splenectomy for hereditary spherocytosis) will falsely raise HbA1C levels

- Iron deficiency anemia is also associated with higher HbA1C levels (RBC production decreases => increased average age of circulating RBCs)

DM: Diagnosis

The Hemoglobin A_{1c} (A1C) test

- A1C is also less reliable than blood glucose measurement in other conditions such as postpartum and HIV treated with certain drugs

DM: Diagnosis

The Hemoglobin A_{1c} (A1C) test

- Marked discordance between measured A1C and plasma glucose levels should raise the possibility of A1C assay interference due to hemoglobin variants (i.e., hemoglobinopathies) and consideration of using an assay without interference or plasma blood glucose criteria to diagnose diabetes

DM: Confirming the Diagnosis

DM: Confirming the Diagnosis

- ***Diagnosis*** **requires** two abnormal test results from the same sample or in two separate test samples ***unless*** there is a clear clinical diagnosis (e.g., patient in a hyperglycemic crisis or with classic symptoms of hyperglycemia and a random plasma glucose ≥200 mg/dL)

DM: Confirming the Diagnosis

- If using two separate test samples, it is recommended that the second test, which may either be a repeat of the initial test or a different test, be performed without delay

DM: Confirming the Diagnosis

- For example, if the A1C is 7.0% and a repeat result is 6.8%, the diagnosis of diabetes is **confirmed**

- If two different tests (such as A1C and FPG) are both above the diagnostic threshold when analyzed from the same sample or in two different test samples, this also **confirms** the diagnosis

DM: Confirming the Diagnosis

- On the other hand, if a patient has discordant results from two different tests, then the test result that is above the diagnostic cut point should be repeated, with consideration of the possibility of A1C assay interference

DM: Confirming the Diagnosis

- The diagnosis is made on the basis of the confirmed test
- For example, if a patient meets the diabetes criterion of the A1C (two results ≥6.5% but not FPG(<126mg/dL), that person should nevertheless be considered to have diabetes

DM: Confirming the Diagnosis

- Since all the tests have preanalytic and analytic variability, it is possible that an abnormal result (i.e., above the diagnostic threshold),when repeated, will produce a value below the diagnostic cut point

- This scenario is likely for FPG and 2-h PG if the glucose samples remain at room temperature and are not centrifuged promptly

DM: Confirming the Diagnosis

- Because of the potential for preanalytic variability, it is critical that samples for plasma glucose be spun and separated immediately after they are drawn

- If patients have test results near the margins of the diagnostic threshold, the clinician should follow the patient closely and repeat the test in 3-6 months

Prediabetes

Prediabetes

- "Prediabetes" is the term used for individuals whose glucose levels do not meet the criteria for diabetes but are too high to be considered normal

Prediabetes

- **Patients with prediabetes are defined by the presence of**
  - **Impaired Fasting Glucose (IFG) (FPG of 100 to 125 mg/dL) *and/or***

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  - **A1C of 5.7 to 6.4%**

Prediabetes

- Note: The World Health Organization (WHO) and numerous other diabetes organizations define the IFG cutoff at 110 mg/dL

Prediabetes

- An estimated 33.9% of U.S. adults aged 18 years or older (84.1 million people) had prediabetes in 2015, and nearly half (48.3%) of adults aged 65 years or older had prediabetes (https://www.cdc.gov/diabetes/data/statistics-report/prevalence.html accessed on 1 December 2019)

Prediabetes

- Prediabetes should not be viewed as a clinical entity in its own right but rather as an increased risk for diabetes and cardiovascular disease (CVD)

Prediabetes

- The continuum of risk is curvilinear, so as plasma glucose or A1C level rises, the diabetes risk rises disproportionately

- Aggressive interventions and vigilant follow-up should be pursued for those considered at very high risk (e.g., those with A1C >6.0%)

Prediabetes

- As noted previously, prediabetes is part of the cluster of conditions termed **'the metabolic syndrome'**

DM: Global Epidemiologic Considerations

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Per Harrison's Principles of Internal Medicine 'PIM' (20th edition, 2018):

- **The worldwide prevalence of DM has risen dramatically over the past two decades, from an estimated 30 million cases in 1985 to 415 million in 2017**

DM: Global Epidemiologic Considerations

Per Harrison's PIM (20th edition, 2018):

- Although the prevalence of both type 1 and type 2 DM is increasing worldwide, the prevalence of type 2 DM is rising much more rapidly, presumably because of
  - increasing obesity
  - reduced activity levels as countries become more industrialized
  - the aging of the population

DM: Global Epidemiologic Considerations

Per Harrison's PIM (20th edition, 2018):

- In 2015, the prevalence of diabetes in individuals aged 20-79 ranged from 7.2-11.4%

DM: Global Epidemiologic Considerations

Per Harrison's PIM (20th edition, 2018):

- Approximately 25% of the individuals with diabetes in the United States were undiagnosed

- Globally, it is estimated that as many as 50% of individuals with diabetes may be undiagnosed

DM: Global Epidemiologic Considerations

Per Harrison's PIM (20th edition, 2018):

- The prevalence of diabetes is similar among men and women, but diabetes-related mortality rates are higher in men compared to women
- The prevalence of DM increases with age

DM: Global Epidemiologic Considerations

Per Harrison's PIM (20th edition, 2018):

- There is considerable geographic variation in the incidence of both type 1 and type 2 DM
  - Currently, Scandinavia has the highest incidence of type 1 DM; the lowest incidence is in the Pacific Rim where it is twenty- to thirtyfold lower; northern Europe and the United States have an intermediate rate

DM: Global Epidemiologic Considerations

Per Harrison's PIM (20th edition, 2018):

- **The prevalence of type 2 DM and its harbinger, IGT, is highest in certain Pacific islands and the Middle East and intermediate in countries such as India and the United States ~ this variability is likely due to genetic, behavioral, and environmental factors**

DM: Global Epidemiologic Considerations

Per Harrison's PIM (20th edition, 2018):

- **DM prevalence also varies among different ethnic populations within a given country, with indigenous populations usually having a greater incidence of diabetes than the general population of the country**

DM: Global Epidemiologic Considerations

Per Harrison's PIM (20th edition, 2018):

- Diabetes is a major cause of mortality
  - In recent years, diabetes has been listed as the seventh leading cause of death in the United States, but several studies indicate that diabetes-related deaths are likely underreported

DM: Global Epidemiologic Considerations

Per Harrison's PIM (20th edition, 2018):

- **Data from the International Diabetes Federation (IDF) suggests that diabetes was responsible for almost 5 million deaths worldwide, accounting for 14.5% of global all-cause mortality in adults aged 20-79 years of age**

DM: Global Epidemiologic Considerations

Per Harrison's PIM (20th edition, 2018):

- Diabetes also has important economic implications
  - In 2015, it was estimated that $673 billion or 12% of health care expenditures worldwide were spent on diabetes (range 5-20%)
  - Up to 75% of individuals with diabetes live in low- or middle-income countries

DM & Prediabetes: Screening

DM & Prediabetes: Screening

- American Diabetes Association (ADA) criteria for testing for diabetes or prediabetes in *asymptomatic* adults

DM/Prediabetes Screening: ADA Criteria

1) Testing should be considered in overweight or obese (BMI ≥25 kg/m^2 or ≥23 kg/m^2 in Asian Americans) adults who have one or more of the following risk factors:
   - First-degree relative with diabetes
   - High-risk race/ethnicity (e.g., African American, Latino, Native American, Asian American, Pacific Islander)
   - History of CVD

DM/Prediabetes Screening: ADA Criteria

- Hypertension (≥140/90 mmHg or on therapy for hypertension)
- HDL cholesterol level <35 mg/dL and/or a triglyceride level >250 mg/dL
- Women with polycystic ovary syndrome
- Physical inactivity
- Other clinical conditions associated with insulin resistance (e.g., severe obesity, acanthosis nigricans)

DM/Prediabetes Screening: ADA Criteria

2) Patients with prediabetes (A1C ≥5.7%, IGT, or IFG) should be tested yearly

3) Women who were diagnosed with GDM should have lifelong testing at least every 3 years

4) For all other patients, testing should begin at age 45 years

DM/Prediabetes Screening: ADA Criteria

5) If results are normal, testing should be repeated at a minimum of 3-year intervals, with consideration of more frequent testing depending on initial results and risk status

DM/Prediabetes Screening

- In patients identified to have diabetes or prediabetes: other cardiovascular disease risk factors should be identified and, if appropriate, treated

Screening for Type 1 Diabetes