Essentials of Diagnosis, Treatment and Prevention of Major Endocrine Diseases: Diabetes Mellitus – 1/2017

LECTURE IN INTERNAL MEDICINE FOR IV COURSE STUDENTS

M. Yabluchansky, L. Bogun, L. Martymianova, O. Bychkova, N. Lysenko, M. Brynza

V.N. Karazin National University Medical School’ Internal Medicine Dept.
Preamble
Internal Medicine Department on Internet: University WEB-portal
Internal Medicine Department on Internet: Facebook
Internal Medicine Department on Internet: Facebook
### Supportive module 1: “Essentials of diagnosis, treatment and prevention of major endocrine diseases”

<table>
<thead>
<tr>
<th></th>
<th>Topic</th>
<th>Credit</th>
<th>Date</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Diabetes. The current classification, etiology, symptoms, diagnosis. Current question of angio-and neuropathy</td>
<td>2</td>
<td>06/09</td>
</tr>
<tr>
<td>2</td>
<td>New methods of treatment for patients with diabetes. Oral hypoglycemic agents, modern insulin and its analogues.</td>
<td>2</td>
<td>13/09</td>
</tr>
<tr>
<td>3</td>
<td>Diseases of the thyroid gland. Goiter: diagnosis, differential diagnosis, prevention and treatment.</td>
<td>2</td>
<td>20/09</td>
</tr>
<tr>
<td>4</td>
<td>Diseases of the adrenal glands. Chronic adrenal insufficiency. Hormonally active tumors.</td>
<td>2</td>
<td>27/09</td>
</tr>
<tr>
<td>5</td>
<td>Diseases of the hypothalamic-pituitary system. Its part in correction of the functional activity of the endocrine glands.</td>
<td>2</td>
<td>04/10</td>
</tr>
</tbody>
</table>
A 62-year-old female with a history of type II diabetes presents to her primary care physician for an annual check-up. Her long-term medications include glyburide, metoprolol, and sertraline. She is afebrile. Blood pressure is 140/90 mmHg, pulse is 82/min, and respiratory rate is 16/min. Fasting glucose is recorded as 160 mg/dL. Serum cholesterol is 150 mg/dL and serum creatinine is 0.9 mg/dL. BMI is 31 kg/m^2. On physical exam, erythema is present at the fifth metatarsal-phalangeal joint of the right foot and the patient has decreased sensation over the affected area.
Which of the following would most likely decrease the incidence of future neuropathy in this patient?

1. Add atorvastatin
2. Add hydrochlorothiazide
3. Right-sided femoral-popliteal bypass
4. Tight glycemic control
5. Discontinue sertraline
TEST - 3

1. Add atorvastatin 2% (3/146)
2. Add hydrochlorothiazide 0% (0/146)
3. Right-sided femoral-popliteal bypass 1% (1/146)
4. Tight glycemic control 96% (140/146)
5. Discontinue sertraline 1% (1/146)

http://www.medbullets.com/step2-3-endocrine/20111/diabetes-mellitus
Plan of the Lecture

- Definition
- Epidemiology
- Mechanisms
- Classification
- Clinical presentation
- Diagnosis
- Treatment
- Prognosis
- Prophylaxis
- Abbreviations
- Diagnostic guidelines

https://1.bp.blogspot.com/-Hb1J2jhUjtE/Td1GcYjbUII/AAAAAAAAA58/bvmJa09k3wU/s1600/Diabetes+mellitus.jpg
Diabetes mellitus (DM) or diabetes is a group of a chronic, often debilitating and sometimes fatal, incurable, costly, and increasing but largely preventable non-communicable metabolic diseases that causes high blood sugar (glucose) levels when the body is unable to produce or/and effectively use insulin with unique multisystem complications of microvascular endpoints, including retinopathy, nephropathy, neuropathy, and macrovascular endpoints in forms of ischaemic heart disease, stroke and peripheral vascular disease).
There are 3 main types of DM:

- **Type 1** (insulin-dependent DM or juvenile DM) results from the pancreas's failure to produce enough insulin,

- **Type 2** (non insulin-dependent DM or adult-onset DM) begins with insulin resistance, when body cells fail to respond to insulin properly,

- **Gestational** occurs when pregnant women without a previous history of DM develop high blood-sugar levels.
Epidemiology 1

• DM is one of the most common endocrine disorders affecting almost 6% of the world's population.

• The number of patients will reach 300 million in 2025 (International Diabetes Federation, 2001).

• More than 97% of these patients will have type II DM.
Epidemiology 2

Prevalence estimates of diabetes, 2025

>300 million diabetics worldwide

Risk Factors 1

Type 1 DM

• Family history

• Environmental factors (exposure to a viral illness)

• The presence of damaging immune system cells (autoantibodies)

• Dietary factors (low vitamin D consumption, early exposure to cow's milk formula, and exposure to cereals before 4 months of age)

• Geography (Finland, Sweden, etc.).

http://www.mayoclinic.org/diseases-conditions/diabetes/basics/risk-factors/con-20033091
Risk Factors 2

Type 2 DM

• Family history
• Race (Blacks, Hispanics, American Indians, Asian-Americans)
• Age (risk increases with age)
• Gestational diabetes
• Polycystic ovary syndrome (women)
• High blood pressure
• Abnormal cholesterol and triglyceride levels.

http://www.mayoclinic.org/diseases-conditions/diabetes/basics/risk-factors/con-20033091
Risk Factors 3

Gestational DM

- Family or personal history
- Race (Black, Hispanic, American Indian or Asian are more likely to develop gestational diabetes)
- Age (women older 25 are at increased risk)
- Weight (being overweight before pregnancy increases risk).
Etiology
Type 1 DM: 1

• Type 1 DM is characterized by loss of the insulin-producing beta cells of the islets of Langerhans in the pancreas, leading to insulin deficiency

• The majority of type 1 DM is of the immune-mediated nature, in which a T-cell-mediated autoimmune attack leads to the loss of beta cells and thus insulin

https://en.wikipedia.org/wiki/Diabetes_mellitus#Type_1
Etiology

Type 1 DM: 2

- Sensitivity and responsiveness to insulin are usually normal, especially in the early stages.
- Type 1 DM can affect children or adults, but was traditionally termed "juvenile diabetes" because a majority of these diabetes cases were in children.

https://en.wikipedia.org/wiki/Diabetes_mellitus#Type_1
Etiology
Type 1 DM: 3

• Type 1 DM can be accompanied by irregular and unpredictable high blood sugar levels, frequently with ketosis, and sometimes with serious low blood sugar levels.

• Type 1 DM is partly inherited, with multiple genes, including certain HLA genotypes, and can be triggered by one or more environmental factors, such as a viral infection or diet (gliadin (a protein present in gluten)).
Etiology
Type 2 DM: 1

• Type 2 DM is characterized by insulin resistance, which may be combined with relatively reduced insulin secretion.
• The defective responsiveness of body tissues to insulin is believed to involve the insulin receptor.

https://en.wikipedia.org/wiki/Diabetes_mellitus#Type_1
Etiology
Type 2 DM: 2

- In the early stage of type 2, the predominant abnormality is reduced insulin sensitivity.
- Type 2 DM is due primarily to lifestyle factors and genetics (obesity, lack of physical activity, poor diet, stress, urbanization)
- Dietary factors also influence the risk of developing type 2 DM (sugar-sweetened drinks, saturated fats, trans fatty acids, white rice).

https://en.wikipedia.org/wiki/Diabetes_mellitus#Type_1
Etiology
Gestational DM: 1

- Gestational diabetes mellitus (GDM) resembles type 2 DM in several respects, involving a combination of relatively inadequate insulin secretion and responsiveness and occurs in 2–10% of all pregnancies.)
Etiology
Gestational DM: 2

- After pregnancy approximately 5–10% of women with gestational DM found to have most commonly type 2 DM
- Gestational DM is fully treatable, but requires careful medical supervision throughout the pregnancy
Etiology

Gestational DM: 3

• Gestational DM can damage the health of the fetus or mother, and risks to the baby include macrosomia (high birth weight), congenital heart and central nervous system abnormalities, skeletal muscle malformations, respiratory distress syndrome, and red blood cell destruction.

https://en.wikipedia.org/wiki/Diabetes_mellitus#Type_1
Mechanisms
Type 1 DM: 1

• Type 1 DM is the culmination of autoimmune inflammatory lymphocytic infiltration with destruction of insulin-secreting beta cells of the islets of Langerhans in the pancreas.

• As beta-cell mass declines, insulin secretion decreases until the available insulin no longer is adequate to maintain normal blood glucose levels type 1 DM.
Mechanisms
Type 1 DM: 2

• After 80-90% of the beta cells are destroyed, hyperglycemia develops and diabetes may be diagnosed

• Polymorphisms of the class II human leukocyte antigen (HLA) genes that encode DR and DQ are the major genetic determinants of type 1 DM.

http://emedicine.medscape.com/article/117739-overview#a3
Mechanisms
Type 1 DM: 3
Mechanisms
Type 1 DM and Neuropathy: 1

• Sensory and autonomic neuropathy in people with DM are caused by axonal degeneration and segmental demyelination

• Many factors are involved, including the accumulation of sorbitol in peripheral sensory nerves from sustained hyperglycemia

• Motor neuropathy and cranial mononeuropathy result from vascular disease in blood vessels supplying nerves.
Mechanisms
Type 1 DM and Neuropathy: 2
Mechanisms
Type 1 DM and Angiopathy: 1

• Microvascular disease causes multiple pathologic complications in people with DM
• Hyaline arteriosclerosis, a characteristic pattern of wall thickening of small arterioles and capillaries, is widespread and is responsible for ischemic changes in the kidney, retina, brain, and peripheral nerves
Mechanisms
Type 1 DM and Angiopathy: 2

- Atherosclerosis of the main renal arteries and their intrarenal branches causes chronic nephron ischemia.
- Vitamin D deficiency is an important independent predictor of development of coronary artery calcification in individuals with type 1 DM.

http://emedicine.medscape.com/article/117739-overview#a3
Mechanisms
Type 1 DM and Angiopathy: 3

Mechanisms leading to microvascular damage

- Normal capillary
  - Increased blood flow to capillaries
  - Advanced glycosylation end products and oxidative stress
  - Loss of pericytes that regulate vessel calibre
  - Thickening and altered composition of the basement membrane

- Basement membrane thickening
  - Capillaries become leaky and don’t function correctly
  - Accumulation of debris within vessels

- Increased vascular permeability
- Capillary closure
  - Tissue beyond the obstruction to become starved of blood and oxygen

https://www.ole.bris.ac.uk/bbcswebdav/institution/Faculty%20of%20Health%20Sciences/MB%20ChB%20Medicine
Mechanisms
Type 1 DM and Nephropathy: 1

• In the kidneys, the characteristic wall thickening of small arterioles and capillaries leads to diabetic nephropathy, which is characterized by proteinuria, glomerular hyalinization (Kimmelstiel-Wilson), and chronic renal failure
Mechanisms
Type 1 DM and Nephropathy: 2

• Exacerbated expression of cytokines such as tumor growth factor beta 1 is part of the pathophysiology of glomerulosclerosis, which begins early in the course of diabetic nephropathy

• Single-nucleotide polymorphisms affecting the factors involved in its pathogenesis appear to influence the risk for diabetic nephropathy in different people with type 1 DM.
Mechanisms
Type 1 DM and Nephropathy: 3

NATURAL HISTORY OF NEPHROPATHY IN TYPE 1 DIABETES

<table>
<thead>
<tr>
<th>Stage</th>
<th>Duration</th>
</tr>
</thead>
<tbody>
<tr>
<td>Normoalbuminuria</td>
<td>15-20 yrs</td>
</tr>
<tr>
<td>Stage of hyperfiltration</td>
<td></td>
</tr>
<tr>
<td>Microalbuminuria</td>
<td>4-5 yrs</td>
</tr>
<tr>
<td>Macroalbuminuria</td>
<td>1 yrs</td>
</tr>
<tr>
<td>Azotemia (Renal failure)</td>
<td></td>
</tr>
<tr>
<td>End stage Renal disease</td>
<td></td>
</tr>
</tbody>
</table>

Mechanisms
Type 1 DM and Nephropathy: 4

- Histological comparison of a healthy glomerulus and a glomerulus in diabetic nephropathy
- One can notice an augmentation of the mesangial matrix

http://dccdn.de/pictures.doccheck.com/images/dd9/5b9/dd95b99fddc71cf75775eb17075da39f52052/m_1407853118.jpg
Mechanisms
Type 1 DM and Nephropathy: 5

- The matrix appears in light pink and has a nodular structure, the capillary lumen is obstructed.
- This condition is called complete glomerular sclerosis.
Mechanisms
Type 1 DM: Double diabetes

In areas where rates of type 2 DM and obesity are high, individuals with type 1 DM may share genetic and environmental factors that lead to their exhibiting type 2 DM features such as reduced insulin sensitivity (double diabetes).
Mechanisms
Type 2 DM: 1

• Type 2 DM is characterized by a combination of peripheral insulin resistance and inadequate insulin secretion by pancreatic beta cells.

• Insulin resistance, which has been attributed to elevated levels of free fatty acids and proinflammatory cytokines in plasma, leads to decreased glucose transport into muscle cells, elevated hepatic glucose production, and increased breakdown of fat.

http://emedicine.medscape.com/article/117853-overview?pa=CgeHjeSgk%2FcDlbsbhmDMA9cE2X%2BmOE54EaA2Xw4hfL8ZpJ81sdgi18ImhYSYbGLT8SlvI8zjYv73GUyW5rsbWA%3D%3D#a3
Mechanisms
Type 2 DM: 2

- A role for excess glucagon cannot be underestimated; indeed, type 2 diabetes is an islet paracrinopathy in which the reciprocal relationship between the glucagon-secreting alpha cell and the insulin-secreting beta cell is lost, leading to hyperglucagonemia and hence the consequent hyperglycemia

- With prolonged diabetes, atrophy of the pancreas may occur
Mechanisms

Type 2 DM: Scheme of abnormal glucose metabolism

http://emedicine.medscape.com/article/117853-overview?pa=CgeHjeSgk%2FcDlbsbhmDMA9cE2X%28mOE54EaA2Xw4hfL8ZpJ81sdgi18lmhYSybGLT8S1v8zjYv73GUyW5rscbWA%3D%3D#a3
Mechanisms
Type 2 DM and Beta-cell Dysfunction: 1

• Beta-cell dysfunction is a major factor across the spectrum of prediabetes to DM
• Beta-cell dysfunction develops early in the pathologic process and does not necessarily follow the stage of insulin resistance
Mechanisms
Type 2 DM and Beta-cell Dysfunction: 2

- Singular focus on insulin resistance as the "be all and end all" is gradually shifting, and hopefully better treatment options that address the beta-cell pathology will emerge for early therapy

http://emedicine.medscape.com/article/117853-overview?pa=CgeHjeSgk%2FcDlbsbhmdMA9cE2X%2BmOE54EaA2Xw4hfl8ZpJ81sdi18ImhYSybGLT8Slv8zjYv73GUyW5rsbWA%3D%3D#a3
Mechanisms
Type 2 DM and Beta-cell Dysfunction: 3

β-CELL FAILURE

- Glucotoxicity
- Lipotoxicity
- Endoplasmic Reticulum Stress
- Mitochondrial Dysfunction
- Oxidative Stress
- Islet Inflammation
- ↑ Islet Amyloid Polypeptide

http://www.intechopen.com/source/html/45317/media/image2.png
Mechanisms
Type 2 DM and Insulin Resistance: 1

• In the progression from normal to abnormal glucose tolerance, postprandial blood glucose levels increase first

• Eventually, fasting hyperglycemia develops as suppression of hepatic gluconeogenesis fails
Mechanisms
Type 2 DM and Insulin Resistance: 2

• During the induction of insulin resistance (such as occurs with a high-calorie diet, steroid administration, or physical inactivity), increased glucagon levels and increased glucose-dependent insulinotropic polypeptide (GIP) levels accompany glucose intolerance

• The postprandial glucagonlike peptide-1 (GLP-1) response is unaltered
Mechanisms
Type 2 DM and Insulin Resistance: 3

• Insulin resistance means the signal insulin gives to a cell is weakened
• This results in less glucose uptake by muscle and fat cells and a reduction in insulin mediated activities inside cells

https://dtc.ucsf.edu/types-of-diabetes/type2/understanding-type-2-diabetes/what-is-type-2-diabetes/
Mechanisms
Type 2 DM and Insulin Resistance: 4

- Compounding this problem of resistance, there is additional defect in insulin production and secretion by the insulin producing beta cells in the pancreas.

https://dtc.ucsf.edu/types-of-diabetes/type2/understanding-type-2-diabetes/what-is-type-2-diabetes/
Mechanisms
Type 2 DM: Genomic factors

- Genome-wide association studies of single-nucleotide polymorphisms (SNPs) have identified a number of genetic variants that are associated with beta-cell function and insulin resistance.
- Some of these SNPs appear to increase the risk for type 2 diabetes.
- Over 40 independent loci demonstrating an association with an increased risk for type 2 diabetes have been shown.

http://emedicine.medscape.com/article/117853-overview?pa=CgeHjeSgk%2FcDlbshmDMA9cE2X%28mOE54EaA2Xw4hfl8ZpJ81sdgi18ImhYSYbGLT8Svl8zjYv73GUyW5rsbWA%3D%3D#a3
Mechanisms
Gestational DM: 1

• If the maternal pancreatic insulin response is inadequate, maternal and, then, fetal hyperglycemia results, that are the most significant source of the accelerated growth exhibited by the fetus.

• Surging maternal and fetal glucose levels are accompanied by episodic fetal hyperinsulinemia.
Mechanisms
Gestational DM: 2

• Fetal hyperinsulinemia promotes excess nutrient storage, resulting in macrosomia. The energy expenditure associated with the conversion of excess glucose into fat causes depletion in fetal oxygen levels that are accompanied by surges in adrenal catecholamines, which, in turn, cause hypertension, cardiac remodeling and hypertrophy, stimulation of erythropoietin, red cell hyperplasia, and increased hematocrit.

http://emedicine.medscape.com/article/127547-overview#a4
Mechanisms

Gestational DM: 3

1. Placenta produces hormones (estrogen, cortisol and human placental lactogen)

2. These hormones inhibit the functioning of insulin

3. Blood glucose level is increased
Classification
American Diabetes Association: 1

• Type 1 DM (β-cell destruction, usually leading to absolute insulin deficiency): immune-mediated, idiopathic
Classification
American Diabetes Association: 2

• Type 2 DM (ranging from predominantly insulin resistance with relative insulin deficiency to predominantly an insulin secretory defect with insulin resistance)
Classification

American Diabetes Association: 3

• Gestational DM (GDM) (diabetes diagnosed in the second or third trimester of pregnancy that is not clearly overt DM)
Classification
American Diabetes Association: 4

• Other specific types of DM: genetic defects of the β-cell, genetic defects in insulin action, diseases of the exocrine pancreas, endocrinopathies, drug- or chemical-induced DM, infections, uncommon forms of immune-mediated DM, other genetic syndromes sometimes associated with DM, impaired glucose tolerance (IGT) and impaired fasting glucose (IFG).
Classification
International Classification of Diseases (ICD): 1

IV Endocrine, nutritional and metabolic diseases
(E10-E14) Diabetes mellitus
E10 Type 1 diabetes mellitus
E11 Type 2 diabetes mellitus
E12 Malnutrition-related diabetes mellitus
E13 Other specified diabetes mellitus
E14 Unspecified diabetes mellitus
Classification
International Classification of Diseases (ICD): 1

XV Pregnancy, childbirth and the puerperium
  O20-O29 Other maternal disorders predominantly related to pregnancy
  O24 Diabetes mellitus in pregnancy
Clinical Investigation
Signs and Symptoms: 1

• The classic symptoms of untreated DM are weight loss, polyuria (increased urination), polydipsia (increased thirst), and polyphagia (increased hunger) that may develop rapidly (weeks or months) in type 1 DM, while they usually develop much more slowly and may be subtle or absent in type 2 DM

https://en.wikipedia.org/wiki/Diabetes_mellitus#Signs_and_symptoms
Clinical Investigation
Signs and Symptoms: 2

• Several other signs and symptoms are not specific to DM and include blurry vision, headache, fatigue, slow healing of cuts, and itchy skin

• Prolonged high blood glucose can cause glucose absorption in the lens of the eye, which leads to changes in its shape, resulting in vision changes

• A number of skin rashes are collectively known as diabetic dermatomes

https://en.wikipedia.org/wiki/Diabetes_mellitus#Signs_and_symptoms
Clinical Investigation

Signs and Symptoms: 3

- Weight Loss
- Extreme Tiredness
- Increased Hunger
- Excessive Thirst
- Frequent Urination

- Tingling and Numbness
- Blurred Vision
- Unhealed Wound
- Urine Attracting Ants

Clinical Investigation

Signs and Symptoms: 4

Diabetes

Central
- Polydipsia
- Polyphagia
- Lethargy
- Stupor

Eyes
- Blurred vision

Systemic
- Weight loss

Breath
- Smell of acetone

Respiratory
- Kussmaul breathing (hyper-ventilation)

Gastric
- Nausea
- Vomiting
- Abdominal pain

Urinary
- Polyuria
- Glycosuria

blue = more common in Type 1

http://www.soccerpluseducation.org/images/treatment-for-type-i-and-type-ii-diabetes-80009.jpg
Clinical Investigation
Diabetic emergencies: 1

• Low blood sugar is common in patients with DM, but most cases are mild and are not considered medical emergencies

• Effects can range from feelings of unease, sweating, trembling, and increased appetite in mild cases to more serious issues such as confusion, aggressiveness, seizures, unconsciousness, and (rarely) permanent brain damage or death in severe cases

https://en.wikipedia.org/wiki/Diabetes_mellitus#Signs_and_symptoms
Clinical Investigation

Diabetic emergencies: 2

• Moderate hypoglycemia may easily be mistaken for drunkenness

• People (usually with type 1 DM) may also experience episodes of diabetic ketoacidosis, characterized by nausea, vomiting and abdominal pain, the smell of acetone on the breath, Kussmaul breathing, and a decreased consciousness

• A rare possibility is hyperosmolar nonketotic state, which is more common in type 2 DM and is mainly the result of dehydration

https://en.wikipedia.org/wiki/Diabetes_mellitus#Signs_and_symptoms
Clinical Investigation

Diabetic emergencies: 3

Low Blood Sugar Symptoms

- Shaking
- Sweating
- Anxious
- Dizziness
- Hunger
- Fast Heartbeat
- Impaired Vision
- Weakness
- Fatigue
- Headache
- Irritable
Diabetic ketoacidosis (DKA)

https://dtc.ucsf.edu/living-with-diabetes/complications/diabetic-ketoacidosis/
Clinical Investigation
Diabetic emergencies: 5

Diagnostic triad of diabetic ketoacidosis (DKA)

http://image.slidesharecdn.com/diabetesketoacidosis-140217063120-phpapp01/95/diabetes-ketoacidosis-4-638.jpg?cb=1392618740
Differences in diabetic ketoacidosis (DKA) and hyperosmolar nonketotic state (HONK)

In DKA:
In the absence of insulin, glucagon inhibits the synthesis of malonyl CoA, resulting in an unregulated entry of fatty acids into the β-oxidation pathway, promoting ketogenesis.

In HONK:
Under the regulatory influence of insulin, malonyl CoA exerts a normal inhibitory effect on the entrance of fatty acids into the β-oxidation pathway, thus limiting ketogenesis.