MEDICINE

432 Team

36 Type 1 Diabetes Mellitus

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COLOR GUIDE: •reference books •Doctor's expanation • Important • additional

Objectives

1. Describe the overview of T1DM and its epidemiology
2. Define etiology and pathophysiology
3. Know the diagnosis and clinical presentation
4. Manage the patients

No slides or objectives were given. The main body of the following notes were compiled from Step Up and Davidson and supplemented by the doctor's notes.

Background: *For your benefit.*

Teddy Ryder, before and after receiving insulin.

Historical background: before insulin was discovered in 1921 -by Frederick Banting and Charles Best, T1DM was fatal. Often killing patients in months' time. It is believed that both Nefertiti and Haroun Al-Rashid died from T1DM. In the past they used primitive methods for diagnosis like smell of ketones and even the sweet taste of urine! Less invasive was observing the way ants collected around the urine of diabetics.

Normal glucose metabolism: Normally you get energy from glucose and store it in the form of fatty and amino acids. Beta cells sense the blood glucose in the blood and secrete insulin accordingly. It decreases blood glucose by allowing its uptake by the tissues and inhibiting hepatic glucose release. Glucose needs insulin to be metabolized and its deficiency means you have to switch to another form of energy. Fat can generate enough energy (9 calories) but the problem is that it has a lot of waste in the form of acidic ketone bodies. It's as if you wanted to make tea and you were out of gas (glucose) so you used wood (fat) instead. It is an inefficient process as it'll generate heat but it'll produce a lot of smoke (ketones). Ketones are very toxic to the brain –which is why it can lead to coma without treatment.

Epidemiology:

The reason T1DM is on the rise is not because of a true increase in the prevalence (109.5 per 100,000 which isn't that common) but because of an increase in birth rate and population size. When they say diabetes is very common they're referring to the rising numbers of T2DM, which accounts for 90-95% of the diabetic population.

Definition and pathophysiology:

- T1DM is a t-cell mediated autoimmune disease that involves destruction of beta cells resulting in *absolute* insulin deficiency.
- Formerly known as insulin dependent diabetes mellitus (IDDM), **patients require insulin to live.**
- Another historical misnomer, juvenile diabetes, refers to its usual incidence peaks in younger people. T1DM can occur at any age and with a more insidious onset. As in latent autoimmune diabetes of adults (LADA), often misdiagnosed for T2DM. Diagnosis can be confirmed by the presence of pancreatic autoantibodies.

- Destruction of beta cells occurs gradually over years. But marked hyperglycemia accompanied by classical symptoms occurs only when 80-90% of beta cells are destroyed.
- It develops in genetically susceptible individuals who are exposed to an environmental factor that triggers the immune response:

1) Genetic predisposition: (HLA DR3/DR4).
2) Environmental predisposition:
   - Suggested by:
     - The concordance rate between monozygotic twins is less than 40%.
     - The seasonal (during the winter months) and geographic (very common in Scandinavian countries e.g.; Finland) variations in incidence.
   - It is hypothesized that environmental factors may trigger T1DM by either:
     - Direct toxicity to beta cells.
     - Stimulating an immune response against beta cells (cross reaction).
   - Potential triggers can be:
     - Viruses (Mumps, Coxsackie B, Rubella).
     - Dietary (cow's milk)

Note(s): *The doctor focused on the link between genetics and immunology.*

T1DM is unique in that it shows you the interplay between genetics and immunology. They found that in T1DM there is a defect in the HLA (located on chromosome 6p) regions DR3 and DR4. The site of specific virus antibodies are located above and below this region. When an infection takes place the neighboring region will also get transcribed and translated. The resulting protein, islet cell antibody, will circulate the blood and result in insulitis. Once beta cells are destructed, they cannot be regenerated. *Occurrence of all these events determines whether an individual will develop the disease or not.*

Q: Is T1DM a genetic disease or a familial disease? *The doctor wants you to know the difference.*

T1DM is NOT familial but genetic. The chances of transference are very low (3% if it's the mother, 9% if it's the father). In contrast, T2DM is a familial (like hemophilia) polygenic (many genes interact) disease you inherit from both parents' genes (resistance gene, obesity gene,…) which come together to manifest the disease.

TABLE 4-3 Comparison of Type I and II Diabetes Mellitus

	Type I	Type II
Onset	Sudden	Gradual
Age at onset	Any age (typically young)	Mostly in adults
Body habitus	Usually thin	Frequently obese
Ketosis	Common	Rare
Autoantibodies	Present in most cases	Absent
Endogenous insulin	Low or absent	Can be normal, decreased, or increased
HLA Association	**Yes (HLA- DQ/DR)**	**No**
Genetic factors	Concordance rate between identical twins is 50%	Concordance rate between identical twins is 90% Therefore, type II demonstrates a much stronger genetic component than type I

Clinical presentation:

- Cardinal symptoms are (polyphagia, polydipsia, polyuria and weight loss).
- Symptoms often develop quickly over days to weeks.
- Sometimes appear after an illness.

Extra: the cause of metabolic disturbance in DM

TABLE 4-5 Symptoms of Diabetes Mellitus

Symptom	Cause
Polyuria	Glucose in renal tubule causes osmotic retention of water, causing a diuresis
Polydipsia	A physiologic response to diuresis to maintain plasma volume
Fatigue	Mechanism unknown, but probably due to increased glucose in plasma
Weight loss	Due to loss of anabolic effects of insulin
Blurred vision	Swelling of lens due to osmosis (caused by increased glucose)
Fungal infections	Fungal infections of mouth and vagina common—*Candida albicans* thrives under increased glucose conditions
Numbness, tingling of hands and feet	Neuropathy Mononeuropathy: due to microscopic vasculitis leading to axonal ischemia Polyneuropathy: etiology is probably multifactorial

Note(s):

Patients will present to the ER immediately. This is in comparison to type 2 wherein they remain asymptomatic for years and complications can be present at the time of diagnosis.

Tests:

- T1DM is a *clinical* diagnosis. You don't need these tests to tell you because the clinical presentation is strong enough to give you the final clue.

Test	What is it?	Sensitivity	Specificity
Random blood glucose (RBG)	A sample is taken without regard to last meal. Usually used for screening.	If –ve you're sure the patient is truly not diabetic (sensitive).	If +ve, you're not sure if the patient is diabetic (not specific).
Fasting blood glucose (FBG)	Patient should be fasting for at least 8 hours. It shows you impaired fasting.	If –ve you're not sure if the patient is truly not diabetic (not sensitive).	If +ve, you are sure the patient is diabetic (specific).
Oral glucose tolerance test (OGTT)	First sample is taken with the patient fasting. Then a glucose load of (75grams) is administered as an oral solution. Another sample is taken 2 hours postprandial. It is often used for research and it shows impaired glucose tolerance.	Both sensitive and specific because you do both a FBG and a postprandial.	
HbA1C	Exposure of hemoglobin A results in nonenzymatic glycation of the protein. It gives the average BG (blood glucose) for the last 3 months – average RBC lifespan. It is beneficial for evaluating control and as of recent is also considered a diagnostic test.		

The doctor explained sensitivity and specificity in detail. Everything else in the table is extra.

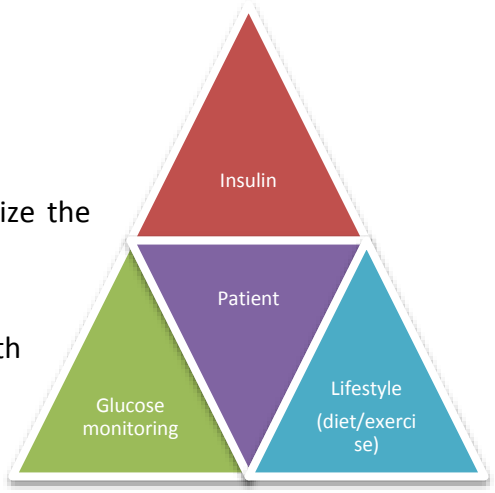
TABLE 4-4 Diagnostic Criteria for Diabetes Mellitus

Glucose Test	Impaired Glucose Tolerance (mg/dL)	Diabetes Mellitus (mg/dL)
Random plasma	—	>200 with diabetic symptoms
Fasting	110–126	>126 on two occasions
2-hr postprandial	140–200	>200
Hemoglobin A1c (%)	5.7–6.4	>6.5

Outlook:

- Diabetes is an issue not because of the disease per se but rather the chronic complications that cause major morbidity and mortality.
    - Complications occur in both in T1DM and T2DM. The reason we see it more in T2DM is because: a) they accounts for the majority of diabetics. b) they're asymptomatic and often present in late phases.
- T1DM poses a huge burden on patient as it interferes with their lifestyle. A patient has to check their BG, inject and follow up at least every 3 months. Very demanding type of disease.
- T1DM is often associated with other autoimmune diseases including thyroid disease, celiac disease, Addison's, pernicious anemia and vitiligo. Patients are usually screened for celiac and thyroid.

Management:



The aims of management are to improve symptoms and minimize the risk of long-term complications.

I. Insulin is the mainstay of treatment.
    - There are 36 existing preparations of insulin with differing profiles (onset, release, duration).
    - Different regimens exist. Some more vigorous than others. Often 2 kinds of insulin are used.
        a) Short acting insulin (bolus): to cover food and highs.
        b) Long acting insulin (basal): to maintain a patient's BG between meals and overnights and counteract hepatic glucose.
    - You can mix and match according to your patients' needs.
    - It is delivered subcutaneously using an insulin delivery system like a syringe, an insulin pen or an insulin pump.

- Insulin pump: A small pager-like computer that continuously delivers insulin through a tube, mimicking normal physiology. Patients can discretely administer boluses. Although with many limitations, it can vastly improve BG control and

offer a better quality of life. Management can be fortified with a continuous glucose monitor that shows BG measurements throughout the day.

II. Education
- A diagnosis of T1DM often entails a steep learning curve.
- You cannot just prescribe insulin to a patient. You must direct the patient to monitor physical activity and diet, correlate with BG readings and adjust the doses accordingly.

III. Physical activity and diet.

- In the old days, insulin started as soluble insulin and NPH. Pancreases were harvested and crushed and insulin was chromatographically separated. It was then linked to zinc to prolong its action. Such crude methods are no longer in use as they cause severe allergic reactions and cannot meet the present demand.
- Current insulin analogues are manufactured using recombinant DNA technology: insulin gene is cleaved and impregnated into e-coli to produce insulin. Profile can be modified with genetic engineering.
- Quality of life has improved significantly with current options but psychosocial barrier remains an issue.

Main types of insulin preparations

Type	Onset	Peak	Duration	Comments
Rapid-acting insulin analogue	5-15 min	30-60 min	2-5 hr	Can be injected at the start of a meal
Short-acting (soluble/regular insulin)	30 min	1-3 hr	4-8 hr	Usually injected 15-30 minutes before a meal. Clear solution
Intermediate or long-acting insulin (isophane or zinc insulin)	1-2 hr (NPH, Lente) 2-3 hr (Ultralente)	4-8 hr 4-8 hr	8-12 hr (NPH) 8-24 hr (Ultralente)	Used to control glucose levels between meals. May be combined with short-acting insulin
Long-acting insulin analogue	30-60 min	No peak	16-24 hr	Usually taken once daily

The doctor did talk extensively about management options but this table and some info about insulin mentioned above is extra.

Future treatments:

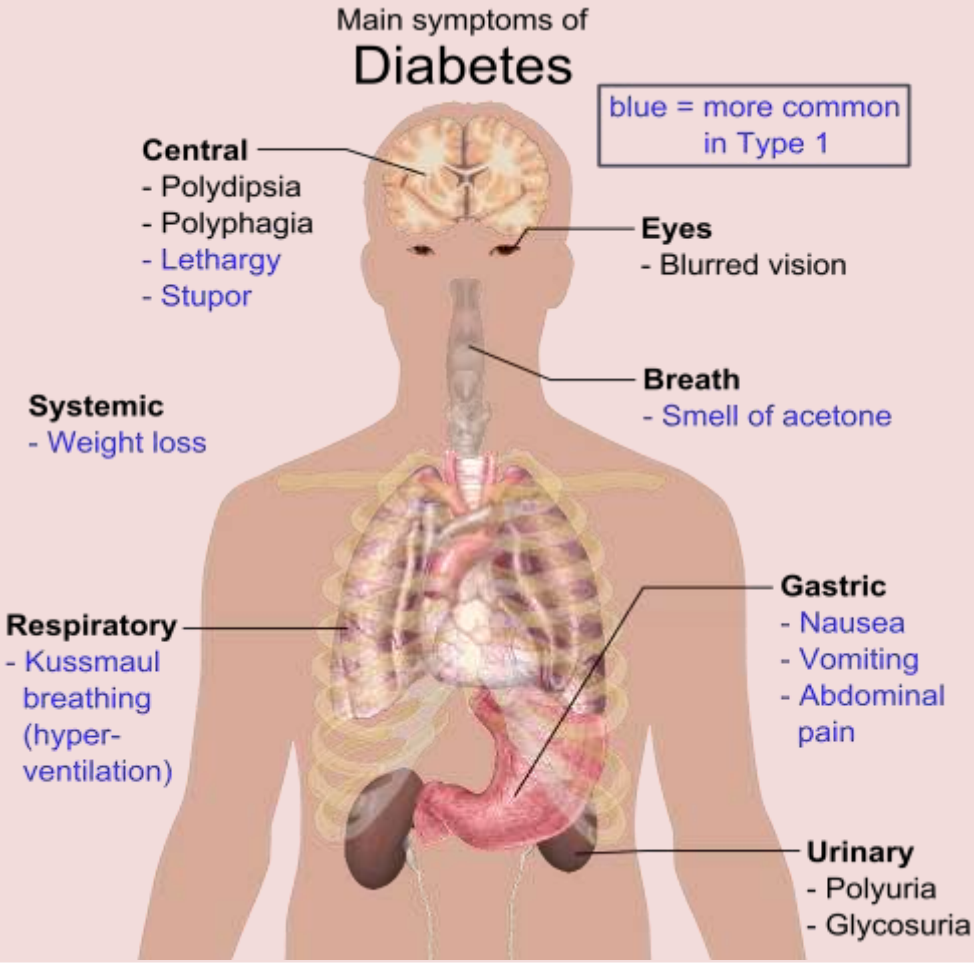
1. A new kind of insulin with particles that bind to it and stop its action when BG falls.
2. Stem cell: The stem cell is a primitive cell that has been harvested and made to differentiate it into a beta cell. Despite the recent advances with this approach, it still remains far from reality. Those *stupid* beta cells do in fact secrete insulin but they do so haphazardly. They do not respond to changes in BG like a normal cell would do but produce insulin blindly, much like the e-coli, causing hypoglycemia. No glucose sensors. The great success is not producing beta cells but in making them sense glucose and suspend production when appropriate.
3. Artificial pancreas: a lot of research goes into developing a closed loop system where an insulin pump and a glucose sensor come together without the need for patient interference. The problem is that there are countless factors that affect a BG and thusly insulin requirements from day to day. Such changes cannot be quantified and that is why you cannot create an algorithm that replaces a patient's judgment.
4. Beta cell transplant: it is reserved for patients with brittle diabetes and those undergoing kidney transplants. The problem is that you need 2 donors, the transplanted cells do not survive more than 5 years and it is not a simple procedure.

Real cases (last 4 from 431 team)

- A type 1 diabetic was traveling to Tabouk and took his shot and then suffered from severe hypoglycemia that resulted in cognitive impairment. He was never the same again.
- A case of T1DM with very labile numbers that the patient could pass out any moment with readings ranging from 600 to 3mg/dL.
- The dr. mentioned that he had a patient one year ago, he was "almost 70 years old" and was diagnosed with type I diabetes. E.g. of LADA! *A very rare case*.
- One of the dr's patients died in a road accident because of a hypoglycemic attack according to his wife who was with him in the car.
- One of the patients was intubated in the ICU for seven days because of severe acidosis "Severe acidosis is very toxic to the brain and the body, people can go into a coma or die from it."
- Classic scenario: A diabetic mother who is busy with her daughter's marriage arrangements will spend almost the whole day with her daughter shopping from one store to another "even if she takes her appropriate dose and balances it with an appropriate diet", she will eventually become hypoglycemic because of the long-duration

SUMMARY

1) You must know about DM because approximately 1 third of your patients will be diabetic.
2) When we talk about DM being on the rise in the kingdom, we are referring to T2DM.
3) T1DM is the more severe type of DM, it accounts for 5-10% of the diabetic population.
4) It results from an interplay of environmental factors and genetic predisposition.
5) HLA regions DR3/DR4 are associated with T1DM.
6) Autoimmune destruction of beta cells result in absolute insulin deficiency. Patients are insulin dependent.
7) T1DM is a clinical diagnosis. Cardinal symptoms are weight loss, polyuria, polydipsia, and polyphagia.
8) The main issue with diabetes is not the disease itself but its complications.
9) Management often involves a multidisciplinary approach of education, diet and medication.
10) The aim of management is to decrease acute and chronic complications
11) T1DM is not curable yet.



General Approach to Diabetes Mellitus

CLASSIFICATION

- **TYPE 1 DIABETES** autoimmune destruction of b cells, prone to DKA
- **TYPE 2 DIABETES** insulin resistance and a relative or absolute insulin deficiency
- **GESTATIONAL DIABETES** glucose intolerance diagnosed during pregnancy

OTHER SPECIFIC TYPES

- **GENETIC DEFECTS OF b CELL FUNCTION**
- **GENETIC DEFECTS IN INSULIN ACTION**
- **OTHER GENETIC SYNDROMES ASSOCIATED WITH DIABETES**
- **DISEASES OF THE PANCREAS cystic fibrosis, hemochromatosis, neoplasia, pancreatitis, pancreatectomy**

There are many other types but to make it short I didn't mention them

CLINICAL FEATURES

HISTORY: duration and type of diabetes, diabetic control (frequency of monitoring, hypoglycemia, hyperglycemia, previous HbA1C, previous DKA, prior hospitalization), treatment (insulin, oral hypoglycemic agents, healthy eating guidelines, exercise, education), acute complications (polyuria, polydipsia, blurred vision, numbness, weight loss, fatigue), chronic complications (see previous section). Risk factors for heart disease (hyperlipidemia, hyperten sion, smoking, family history of early cardiac events, obesity)

PHYSICAL: height, weight, BMI, vitals, fundi (diabetic or hypertensive retinopathy, cataracts), thyroid, chest, cardiac, abdominal examination, insulin injection sites, peripheral pulses, check for carotid and femoral bruits, diabetic foot examination including neurological examination

INVESTIGATIONS

BASIC: **LABS** glucose, lytes, anion gap, osmolality, ketones, creatinine, urea, HbA1C, fasting lipids, ALT, ALP, CK, TSH, C peptide, urine albumin to creatinine ratio

SPECIAL: ANTIBODIES insulin antibody, GAD65 antibody, islet cell antibody

MANAGEMENT OF DKA

SYMPTOM CONTROL:

- **ACUTE** ABC, O2, IV, may need intubation
- **CORRECT** ACID/BASE ELECTROLYTES ABNORMALITIES
- **MONITOR** continuous cardiac monitor until patient is stable. Create flow sheet with time vs. pH, lytes, anion gap, ketones, glucose, insulin, IV fluids. Careful monitoring and frequent reassessment is required
- **HYDRATION** NS 15 20 mL/kg/h IV bolus to fluid resuscitate then decrease IV accordingly
- **POTASSIUM** once serum K is <5.0 mEq/L and patient is voiding, add supplemental KCL (see table on next page)
- **INSULIN** give 0.1 units/kg of regular insulin IV push, then 0.1 units/kg/h (mix 25 units of regular insulin in 250 mL D5W. One unit of insulin is equal to 10 mL of drip).
- **GLUCOSE** once serum glucose is less than 15 mM, add glucose to IV fluids (e.g. D5NS, D5½NS). If patient is euvolemic and serum sodium is normal or high, D5½NS should be used

TREAT UNDERLYING DM type.

Questions

1) A 27 y/o female presents to the emergency room with blurry vision, increased urination and increased thirst. She is mildly overweight. She also says she has been eating much more lately but has actually lost weight over the last several months. Her family history is remarkable for celiac disease in her sister and T2DM in her maternal aunt. Her vitals are within normal limits and a P/E is normal. Lab shows a FBG of 210mg/dL. A blood test is +ve for glutamic acid decarboxylase antibodies. What is the best initial treatment for this patient?
   a. Insulin
   b. Rosiglitazone
   c. Diet and exercise
   d. Exenatide

2) A 35-year-old man with a 10-years history of type 1 diabetes mellitus is evaluated because of recent onset of morning hyperglycemia. His home blood sugar logs over the last 10 days have consistently been showing elevated sugars in the range of 220 to 300 mg/dL in the early morning (pre-breakfast) and hypoglycemia at 3:00am. He has also experienced nightmares recently. He has been compliant with his diet instructions and has not changed his dinner potions recently. He takes mixed insulin regimen: NPH/Regular insulin 70/30 mix at 30 units in the AM before breakfast and 20 units in PM 30 minutes before dinner. Which of the following best explains this patient's morning hyperglycemia and how best to manage it?
   a. Dawn phenomenon: increase PM insulin dose
   b. Somogyi effect: increase PM insulin dose
   c. Dawn phenomenon: decrease PM insulin dose
   d. Somogyi effect: decrease PM insulin dose

Answer key:

1. (a): This patient suffers from LADA, evident by presence of autoantibodies. Must use insulin.
2. (d): A distinction must be made between dawn phenomenon and Somgyi effect. Both cause morning hyperglycemia and if present, check glucose at 3:00am to determine the cause. Dawn phenomenon is probably due to an increase in nocturnal secretion of growth hormone. Both 3:00am and 7:00am readings will show hyperglycemia. Treated by increasing evening dose. The Somogyi effect is a rebound response to nocturnal hypoglycemia where counterregulatory mechanisms are activated, leading to morning hyperglycemia. Increasing insulin dose can make the problem worse. As suggested by the nocturnal symptoms and her logs, this patient suffers from Somogyi effect best treated by decreasing evening dose.

432 Medicine Team Leaders

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