Team Medicine

Lecture Number#8

Lecture Title:

Diabetes Mellitus Type 1

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** Note: The lecture was explained without using a PowerPoint Presentation.*

Functional Physiology:

For your understanding

Role of insulin in your body:

- Insulin is secreted from pancreatic B cells into portal circulation.. In response to rise in blood glucose → Insulin is released → suppressing gluconeogenesis + promoting glycogen synthesis and storage.

- Metabolic actions of insulin:

Increase (anabolic effects)	*Decrease (anticatabolic effects)*
Glucose transport to muscles and adipose tissue. "By GLUT 4"	Gluconeogenesis
Glucose phosphorylation.	
Glycogenesis	Glycogenolysis.
Glycolysis	
Triglyceride synthesis	Lipolysis
Fatty acid synthesis (liver)	Fatty acid oxidation (liver) and ketogenesis
Lipoprotein Lipase activity (adipose tissue)	Lipoprotein Lipase (muscle)
Amino Acid transport	
Protein synthesis	Protein degradation

Useful Links:

http://www.dnatube.com/video/8349/Animation-in-3D-of-the--Insulin-processes-mechanism

http://www.youtube.com/watch?v=X0ezy1t6N08

Diabetes Mellitus:

- Diabetes mellitus is a clinical syndrome characterized by hyperglycemia caused by absolute or relative deficiency of insulin.

- Lack of insulin affects the metabolism of carbohydrates, protein, fat and can cause significant disturbances of water and electrolyte homeostasis.

- Long standing metabolic derangement is associated with functional and structural changes in many organs, particularly those of the vascular system, which lead to the clinical 'complications' of diabetes.

- The incidences of both type I and type II diabetes are rising; it is estimated that, in the year 2000, 171 million people had diabetes, and this is expected to double by 2030.

- Type I diabetes is more common in Caucasian populations and in northern Europe; its prevalence in children has doubled in the last 20 years with a particular increase in children under 5 years of age.

(Davidson's p.798-799)

Prevalence of diabetes mellitus in Saudi Arabia:

- Saudi Arabia has one of the highest percentages of Diabetes in the world, with an estimated number of 2,065,300 people diagnosed with the disease by 2010, which is 16.8% of the population (although some studies have shown this percentage to be higher).
http://www.mtholyoke.edu/~cantl20a/classweb/rosewebsite/saudiarabia.html

- This next study was conducted in the years 2001-2007 with the objective of establishing the prevalence of diabetes mellitus type I in Saudi Arabian children and adolescents:

http://www.ncbi.nlm.nih.gov/pubmed/18813413

Diabetes Mellitus Type I:

* Type I diabetes was previously termed 'insulin-dependent diabetes mellitus' (IDDM) and is invariably associated with profound insulin deficiency requiring replacement therapy.

* Type I diabetes is a T cell-mediated autoimmune disease involving destruction of the insulin-secreting β cells in the pancreatic islets, which takes place over many years. Hyperglycemia accompanied by the classical symptoms of diabetes occurs only when 70-90% of β cells have been destroyed.

* Patients with type I diabetes present when progressive β-cell destruction has crossed a threshold at which adequate insulin secretion and normal blood glucose levels can no longer be sustained. Above a certain level, high glucose levels may be toxic to the remaining β cells so that profound insulin deficiency rapidly ensues.

* Hyperglycemia leads to glycosuria and dehydration, which in turn induces secondary hyperaldosteronism.

* Unrestrained lipolysis and proteolysis result in weight loss, increased gluconeogenesis and ketogenesis.

* Ketoacidosis occurs when generation of ketone bodies exceeds the capacity for their metabolism.

* Elevated blood H^+ ions drive K^+ out of the intracellular compartment, while secondary hyperaldosteronism encourages urinary loss of K^+

Symptoms of type I diabetes: “shown in the figure”
Patients usually present with a short history (typically a few weeks)..
(Davidson’s p.800-801)

Doctor's notes:

- Why diabetes is really important?

- Because approximately 1/3 of the patients you will see in your life are diabetics, the other reason is that diabetes is considered a very rapidly growing disease, in addition to being a mysterious disease that can't really be defined, e.g. you can have diabetes with normoglycemia / you can have diabetes with hyperinsulinemia. Although diabetes is classified into type (I, II), gestational diabetes and impaired glucose intolerance, we don't consider it a really good classification! Why is that? Because a lot of patients diagnosed as type I diabetes could develop type II diabetes with time or some can be diagnosed as type II diabetes but eventually become type I.

- Type I diabetes constitutes about 10% of the total diabetic patients.

- Type I diabetes is considered the most aggressive type of diabetes.

- Type I diabetes typically presents in childhood or early adult life. (The earliest type of diabetes)

- Type I diabetes is totally dependent on insulin therapy.

- Type I diabetes is an acute type of disease that presents with a classical presentation [weight loss > fatigue> abdominal pain> nausea and vomiting > ER]. On the other hand, Type II diabetes is usually discovered by chance and is often present for many years before being diagnosed.

- There is a certain criteria 'which tells us what is type I diabetes' and also differentiates between type I and type II diabetes. Why is it important to know that? Because the managements of both diseases are totally different!

Doctor's notes:

Epidemiology:

- The increase of type I DM is explained by the increase of birth rate in KSA (400-500,000/year) not by the prevalence of the disease itself.

Pathology:

- Human leukocyte antigen 'HLA' is present on the short arm of chromosome 6 or as the dr. likes to call it "Ministry of health". Doing an HLA typing test identifies different sorts of diseases.

- The short limb of chromosome 6 will plan what certain diseases you are most likely to develop. E.g. SLE, chron's disease, Type I diabetes and ankylosing spondylitis.

- Type I diabetes occur at a specific section of the gene which is DR3/DR4, so when the mRNA reads this specific segment, it will produce islet cell antibody "ICA" which is an antibody produced against the Beta cells.

- So ICA will be produced > goes through the blood circulation > eventually reaches the pancreas and destroys the beta cells or will induce insulitis "inflammation of beta cells and destruction" and this is why it is considered an acute disease where patients suddenly develop a drop in insulin levels and their blood sugar goes up.

- When you screen for DR3/DR4, you will find that some of the population is carrying it without showing the disease. This tells us that even if you have the gene, that doesn't mean you have type I diabetes. This gene must be stimulated and antibodies must be present for the disease to occur and this is why type I diabetes usually occurs in the first phase of life.

- The other type is the late onset immune disease (Latent autoimmune diabetes of adults) "LADA", which is type I diabetes in adults above 25 years of age.

Doctor's notes:

Definition Criteria for type I diabetes mellitus:

- Genetic Disease.
- Immunological disease.
- Happens at a younger age.
- Total destruction of beta cells.
- DKA "Diabetes Ketoacidosis"

The next special feature about type I diabetes is what we call Diabetes ketoacidosis "DKA":

How do patients develop DKA in type I diabetes?

- Because of insulin lack, the energy is produced by fatty acids and these fatty acids produce a lot of acetone bodies, which are considered the reason behind DKA.

- In type II diabetes, DKA doesn't occur, because patients have enough reserve to prevent ketoacidosis.

- Not like type II diabetes, Type I is not a familial disease. In type II diabetes: (A person who has parents with no diabetes has a ~ 5% chance of developing the disease. If one of his parents has diabetes he has a ~ 15% chance of developing diabetes. But if both of his parents have diabetes he has a ~ 45% chance of becoming diabetic.)

This rapid increase of the disease over the last decades indicates that environmental factors must play an important role in the disease process:

- Viral infections (Mumps and group B coxsackieviruses) can contribute to type I diabetes in humans. ***May trigger the production of ICA*** but as the dr. mentioned previously, not everyone with ICA will develop type I diabetes, there must be certain factors to destruct the beta cells completely.

What is the story of developing severe hyperglycemia in type I diabetes?

- Normally Beta cells produce insulin. In a case of severe hyperglycemia, a sudden drop in insulin and a sudden increase in blood sugar occur.

- The duration between beta cells destruction and severe hyperglycemia is usually days to weeks.

- *In type II diabetes, the duration is much longer (could extend to 10 years) and patients develop what we call insulin resistance at the peripheral level.

Doctor's notes:

Don't forget that diabetes type I is an autoimmune disease.

- Type I diabetes can be a single disease or can be associated with different autoimmune diseases like hyperthyroidism, hyperparathyroidism, pernicious Anemia.. *Must screen for other autoimmune diseases*

- Vitiligo is an autoimmune disease that can be associated sometimes with type I diabetes. [Antibodies are produced against melanocytes leading to destruction of these cells; it has the same mechanism as type I].

Diagnosis of type I diabetes: -

- The best tool is to test the "random blood glucose level".

- Symptoms usually precede the hyperglycemia "Good sign" but it is an acute process, it depends on how frequent you notice the symptoms.

- Symptoms include: [polydipsia, polyuria, polyphagia, weight loss and blurry vision, severe abdominal pain, nausea and vomiting].

- Most of the patients present with DKA.

- So basically we depend on the hematology and the symptoms in diagnosing type I diabetes.

- You may need sometimes to measure the insulin level and c-peptide to distinguish between the two types if the case was not really clear.

- Follow up is by monitoring HbA1c.

Complications: -

- **Acute**:

- 1) Hyperglycemia usually presents as diabetes ketoacidosis "DKA" [Due to two factors]:

- A) **Increased Insulin requirement:** patient goes into stress due to any infection so his insulin requirements increase, while the amount of insulin production in his body stays the same. "Relative Hypoinsulinemia"

- B) **When the patient stops insulin treatment:**
  For example, a student decides to omit the dose the night before her exam, so she could get a sick leave, as a result she will get DKA.

Doctor's notes:

- The mortality from DKA is about 30%. [If the PH is less than 6.5 then the chance of this patient dying is almost 20-30%]

- Nowadays with the new emergency care systems, we rarely see such cases "PH less than 6.5" but it still happens [E.g. from the 17,000 diabetic patients > 1700 will have type I diabetes > 20% of the adolescents will probably develop DKA > 10 % of them will go into severe acidosis *need to take care of those patients*]

- **How do we manage DKA?**

- **IV FLUIDS ******,** because they usually die from hypovolemia and cardiogenic shock. [So fluids are really given to treat the case.]

- **Then we give insulin,** to stop the formation of ketone bodies.

- **Add K+ into the Iv fluids;** patients tend to loose potassium in their urine so they can develop severe hypokalemia that induces arrhythmias.

- 2) Hypoglycemia [Hypoglycemia is more frequent and it is life threatening]:

- The most common acute complication.

- Causes:

- High dose of insulin.

- Not enough food (diet).

- Exercise and no balanced diet. [There should be a balance between the physical activity and the diet]

- [E.g. Patients who take their doses of insulin without eating food "not balanced diet" will probably develop hypoglycemia]

- **Chronic:**

- [Separate Lecture]

Doctor's notes:

Management:

- In the beginning, insulin was brought from animal sources [regular or soluble insulin] then protamine zinc was added which made the half-life of insulin longer.

- Regular insulin: [usually acts within minutes "finishes its effect within 12-15 minutes].

- NPH insulin: (protamine zinc insulin) [acts within hours].

- The used types of insulin now are [Rapid-acting, Short- acting, Intermediate and Long-acting (Lantus and Levemir).]

- Now insulin can be given at night (Long-acting) or with each meal. Also, we can even teach patients how to calculate the amount of carbs needed between doses.

- Back then when insulin was extracted from animals, it used to cause a lot of allergies, now with the human insulin, we don't see a lot of allergies because of its better efficacy and quality.

- Many patients use Insulin pump; it gives them the normal basal insulin as the pancreas. They should measure the required dose before each meal using carbohydrates counting.

- **Pancreas transplantation:**

- It's a tool rarely used but sometimes it is considered a life saving procedure.

- A pancreas transplant can cure diabetes and eliminate the need for insulin shots. Because of the risks involved with surgery, most persons with type 1 diabetes do not have a pancreas transplant just after they are diagnosed.

- Pancreas transplantation "Whole organ", started in fact in the 60's, but in one of the cases, they found the patient later on with peritonitis because the exocrine function of the pancreas was compromised.

- Patients who undergo whole organ transplantation need immunosuppressive agents. "Many complicated side effects"

- Pancreas transplant is rarely done alone. It is almost always done when someone with type 1 diabetes also needs a kidney transplant.

- Islet cell transplantation:

  "Is the transplantation of isolated islets from a donor pancreas and into another person. It is an experimental treatment for type 1 diabetes mellitus. Once transplanted, the islets begin to produce insulin, actively regulating the level of glucose in the blood."

- The pancreas is usually crushed by using digestive enzymes to separate the beta cells from the exocrine part, then the islets are fused into the patient's liver.

- There are three major problems "restrictions" associated with islet cell transplantation:

- Two donors are needed for the transplantation. This is due to the loss of more than 50% of the beta cells during the purification and separation.

- You have to use immunosuppressive agents.

- They found that over 3-5 years after transplantation, the newly planted beta cells start dying slowly.

Real CASES ⓘ:

- 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 a 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 activity.

HLA and DMT1:

REMEMBER

- A histocompatibility antigen blood test looks at proteins called human leukocyte antigens (HLAs). These are found on the surface of almost all cells in the human body. HLAs are found in large amounts on the surface of white blood cells. They help the immune system tell the difference between body tissue and substances that are not from your own body.
- Over 20 different regions of the human genome show some linkage with type I diabetes but most interest has focused on the human leucocyte antigen (HLA) region within the major histocompatibility complex on the short arm of chromosome 6; this locus is designated IDDM 1.

History ⓘ:

- Type I diabetic patients used to die before the discovery of insulin by Banting and Best in 1921.

** What is the interesting story behind the discovery of insulin?

In the fall of 1920 Dr. Frederick Banting had an idea that would unlock the mystery of the dreaded diabetes disorder. Before this, for thousands of years, a diabetes diagnosis meant wasting away to a certain death. Working at a University of Toronto laboratory in the very hot summer of 1921 Fred Banting and Charles Best were able to make a pancreatic extract which had anti diabetic characteristics. They were successful in testing their extract on diabetic dogs. Within months Professor J. J. R. MacLeod, who provided the lab space and general scientific direction to Banting and Best, put his entire research team to work on the production and purification of insulin. J.B. Collip joined the team and with his technical expertise the four discoverers were able to purify insulin for use on diabetic patients. The first tests were conducted on Leonard Thompson early in 1922. These were a spectacular success. Word of this spread quickly around the world giving immediate hope to many diabetic persons who were near death. A frenzied quest for insulin followed. Some patients in a diabetic coma made miraculous recoveries.

- Harun al-Rashid died of type I diabetes at age 36. His physician discovered by smelling the urine that contained ketone bodies that is it was actually DKA "Diabetes ketoacidosis" that caused his death. **DMT1 is the only disease that can be diagnosed by smelling the urine due to the presence of acetones bodies.

Banting, right, and Best, left, with one of the diabetic dogs used in experiments with insulin.
Credits: University of Toronto Archives.

Management:

- How do Beta cells behave normally?

- Eating a piece of chocolate > pancreas will release insulin on two phases [phase 1 and phase 2] phase 2 depends on the message the pancreases receives from the gut and this message depends completely on the amount and the volume of food. If you eat a diet that contains only sugar the process of releasing insulin will rely mainly on phase 1 but if you eat a diet that contains proteins and fat more, it will rely on phase 2 > so insulin therapy must be decided from this point of view.

- Back in the 80s, only two types of insulin were discovered.

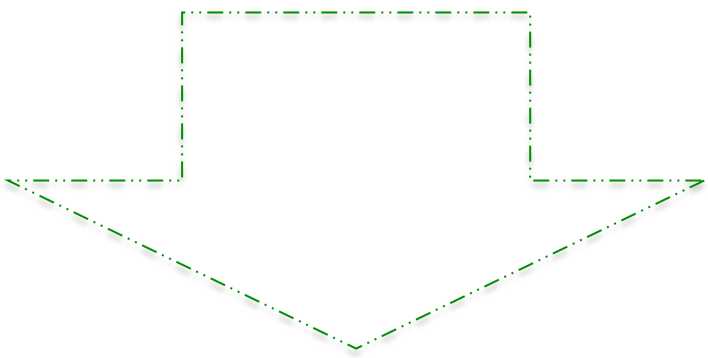
- After human insulin was discovered, we now have four major types of insulin that can cover professionally the patients' requirements.]

- The History of insulin:

  http://www.med.uni-giessen.de/itr/history/inshist.html

For more clarification

The following chart lists the types of injectable insulin with details about **onset** (the length of time before insulin reaches the bloodstream and begins to lower blood sugar), **peak** (the time period when the insulin is the most effective in lowering blood sugar) and **duration** (how long insulin continues to lower blood sugar). These three factors may vary, depending on your body's response. The final column provides some insight into the "coverage" provided by the different insulin types in relation to mealtime:



Type of Insulin & Brand Names	Onset	Peak	Duration	Role in Blood Sugar Management
Rapid-Acting				
Humalog or lispro	15-30 min.	30-90 min	3-5 hours	Rapid-acting insulin covers insulin needs for meals eaten at the same time as the injection. This type of insulin is often used with longer-acting insulin.
Novolog or aspart	10-20 min.	40-50 min.	3-5 hours	
Apidra or glulisine	20-30 min.	30-90 min.	1-2½ hours	
Short-Acting				
Regular (R) humulin or novolin	30 min. -1 hour	2-5 hours	5-8 hours	Short-acting insulin covers insulin needs for meals eaten within 30-60 minutes
Velosulin (for use in the insulin pump)	30 min.-1 hour	2-3 hours	2-3 hours	
Intermediate-Acting				
NPH (N)	1-2 hours	4-12 hours	18-24 hours	Intermediate-acting insulin covers insulin needs for about half the day or overnight. This type of insulin is often combined with rapid- or short-acting insulin.
Long-Acting				
Long-acting insulin covers insulin needs for about one full day. This type of insulin is often combined, when needed, with rapid- or short-acting insulin.	Lantus (insulin glargine)	1-1½ hour	No peak time; insulin is delivered at a steady level	20-24 hours
	Levemir (insulin detemir)	1-2 hours	6-8 hours	Up to 24 hours
Pre-Mixed*				
Humulin 70/30	30 min.	2-4 hours	14-24 hours	These products are generally taken two or three times a day before mealtime.
Novolin 70/30	30 min.	2-12 hours	Up to 24 hours	
Novolog 70/30	10-20 min.	1-4 hours	Up to 24 hours	
Humulin 50/50	30 min.	2-5 hours	18-24 hours	
Humalog mix 75/25	15 min.	30 min.-2½ hours	16-20 hours	
*Premixed insulins are a combination of specific proportions of intermediate-acting and short acting ins.				

Summery

- Type I diabetes is a genetic disease, unlike type II which is a familial disease.
- Type I diabetes constitutes about 10% of the total diabetic patients.
- Type I diabetes is considered the most aggressive and acute type of diabetes.
- Type I diabetes typically presents in childhood or early adult life. Type I diabetics are usually thin unlike type 2.
- Type I diabetes classical presentation: [weight loss > fatigue> abdominal pain> nausea and vomiting > ER].
- Type I diabetes occur at a specific section of the gene which is DR3/DR4, but it needs to be activated. It is activated by environmental factors (Coxsackie virus in example).When activated it produces ICA. And if ICA reaches the pancreas the beta cells will be destroyed and no insulin will be produced.
- Definition Criteria for type I diabetes mellitus:
  - Genetic Disease.
  - Immunological disease.
  - Happens at a younger age.
  - Total destruction of beta cells.
  - DKA “Diabetes Ketoacidosis”.
- The best tool for diagnosis is the “random blood glucose level”.
- HBA1c is for monitoring only.
- Most patients present with DKA.
- Acute Complications of diabetes type I:
  - 1- Hyperglycemia (DKA): it is caused by either increase demand of insulin in stress situations or if the patients stops insulin therapy. It is a dangerous situation with a high mortality. However management is simple with IV fluids (with K) and then Insulin.
  - 2-Hypoglycemia: the most common complication and it is also life threatening. It is caused by decreased diet, increased insulin or increased exercise.
- Management: Insulin is the mainstay for type I diabetic patients. Insulin now has various types and is used in a variety of manners.
- Pancreas transplantation is rarely done but could be a lifesaving operation especially in patients who need kidney transplantation as well.
- Islet cell transplantation is an experimental treatment that could be promising in the future, however it has some restrictions.

Questions

1- The best test to diagnose a patient with suspected insulin-dependent diabetes is:
   A- Glycated hemoglobin (HB A1C)
   B- Random Blood Glucose
   C- Urine Glucose Dipstick

2- A 37-year-old male patient presented to the emergency department at 2 AM with vomiting and abdominal pain. He had a 2-week history of polyuria and polydipsia, accompanied by a 20-pound weight loss and blurred vision. His medical history was unremarkable, except for being treated for hypertension with amlodipine 10 mg daily, which provided good control. (His blood pressure on admission was 135/80.)
   Results of hospital laboratory studies revealed that the patient's initial blood glucose level was 342 mg/dL and Ph was 7.19. The patient reported no family history of diabetes.

   What is your initial step in management?

   A- IV Insulin Therapy
   B- Oral Hypoglycemic agents
   C- IV fluids with Potassium
   D- IV fluids without Potassium

3- A 20 year old male diagnosed with type 1 diabetes was brought to the emergency department at 9 AM by his brother. He was unconscious and was obviously sweaty. When you asked his brother about his medications and diet he told you that he took his insulin injection in the morning but did not have breakfast this morning because he woke up late for his college. What do you think was the cause of his unconsciousness?
   A- Diabetic Ketoacidosis
   B- Hypoglycemia due to decreased diet
   C- Diabetic Neuropathy
   D- Hypoglycemia due to insulin overdose

Answers : B-C-B

Explanation :

1- Glycated hemoglobin (HB A1C) is incorrect because it takes a very long time to be elevated, that’s why it is better used in monitoring treatment.
   Random Blood Glucose is the method of choice.
   Urine Glucose Dipstick is not used for diagnosis because blood glucose may be elevated but still did not reach the renal threshold.

2- This is a typical presentation of DKA, patients with DKA usually die because of hypovolemia and cardiogenic shock, and moreover they lose a lot of potassium in urine. Restoring the fluids is the most important step in

managing a patient with DKA, however, if you do not give the patient potassium he might develop arrhythmias due to hypokalemia. So the initial step is IV fluids which include potassium.

3- Hypoglycemia is the most common complication of type 1 diabetes. In this case the patient has taken his insulin but did not eat after it. This will allow the insulin to work without any oral glucose intake, which will cause hypoglycemia. Unconsciousness and sweating are two common symptoms of hypoglycemia.