Lipid Disorders
الفريق الطبي الأكاديمي

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Last lecture we talked about the lipoprotein metabolism, you saw how these lipoprotein particles help transport different lipids to different tissues to do functions.

In this lecture you’ll have some applications on what we get in last one, get ready, drink Nescafé and let’s start by the name of Allah 😃:

*These are the normal physiological concentrations of different lipid parts:

**Levels of Plasma Lipids**

- **LDL**
  - < 100 → Optimal
  - 100-129 → Near optimal
  - 130-159 → Borderline
  - 160-189 → High
  - ≥ 190 → Very High
- **Total Cholesterol**
  - < 200 → Desirable
  - 200-239 → Borderline
  - ≥ 240 → High
- **HDL**
  - < 40 → Low
  - ≥ 60 → High
- **Serum Triglycerides**
  - < 150 → normal
  - 150-199 → Borderline
  - 200-499 → High
  - ≥ 500 → Very High

How can these values be useful?!

When you have a patient and you are suspecting of lipid metabolism disease or disorder, after examination you ask
the patient for some blood tests and usually the blood tests include the lipid profile which consists of the concentration of triglyceride, LDL, HDL and sometimes glycoproteins concentrations or in some people Eco protein concentrations.

“So these values are very important to you by time you’re going to memorize them but for the time then they’re given to you as handouts and the laboratory requests usually these values are given to guide you and help you to take your decision”

For example: the [LDL] must be less than 100 mg/dl. In Jordan most of people have LDL above this value because they “we” eat a lot of “منسف” and other things. So when you have the results of that patient you have to study them very well and that’ll help you in diagnosis for the lipid disorder, OK!

**The doctor read the values in the slide and then said: HDL must be >60 and the abnormal value is less than 40. So these values you are going to use to interpret the results of the blood testing after you request a blood test for the patient to suspect that patient to have some of the lipid disorder.

Like what lipid disorders?!
- Hypercholesterolemia
- Hyperchylomicronemia
- Hyper"اللي اخدناهم كل ال
In the next few slides there are some examples and classifications for the dyslipidemia (lipid disorders) which means abnormal values of the lipids and lipoproteins. We can have hypolipoproteinemia or hyperlipoproteinemia and that is related to the particles themselves or to the Eco proteins that are disattached to the lipid particles.

**DYSLIPIDEMIA**

Dyslipidemia (elevated blood lipid and lipoproteins [ ])s has several forms:
- Hyperlipidemia: elevated blood TG & cholesterol
- Hypertriglyceridemia: elevated TG only
- Hypercholesterolemia: only elevated blood cholesterol concentrations
- Hyperlipoproteinemia: elevated lipoprotein concentrations

So these are the dyslipidemia which are defined as high levels of lipids + high levels of lipoproteins
*High level of glyceride is a one type of dyslipidemia

*High level of cholesterol → hypercholesterolemia

*Elevated values of lipoproteins → hyperlipoproteinemia

So elevation of lipoproteins and lipids parameter (triglyceride, cholesterol, LDL, HDL and so on) is classified as hyperlipidemia and hyperlipoproteinemia.

This table is very important and there will be very advantages to you if you understand it and then memorize it “the doctor’s advice”

*The first column gives you the type of the hyperlipidemia of the dyslipidemia the patient has.

What are the characteristics of the types of hyperlipidemia?!

**Type I:

You’ll see high chylomicrons
How do we know that the patient has high chylomicrons?!
If you take blood sample from the patient you’ll see milky blood and that indicates (especially if the patient is fasting for at least 12-14 hours) that the patient has hyperchylomicrons (chylomicronemia)

**NOTE:** generally for any testing of lipids in blood the patient must be fasting at least 12-14 hours to have re.

As we know the chylomicrons are rich with cholesterol and triglyceride so you will see more than 1000 mg of triglyceride in Hyperchylomicronemia.

What is the triglyceride?!
Is a storage material of lipids in fat cells which is composed of glycerol attaches with 3 fatty acids.

Why 3 fatty acids not 4 for example?!
Because glycerol has 3 hydroxyl attaches to 3 carbon atoms.

You will see xanthoma, what is it?!
Is the presence of the lipid in the skin so you can see what is called eruptive xanthoma because lots of excess lipids mainly triglyceride in the skin cells.

**Type IIa:**
Here the lipoprotein LDL is defected which is rich with cholesterol.

So if you take blood sample of that patient and essay of cholesterol it’ll be above the physiological concentration that will confer your suspected diagnosis that this patient has type 2a hyperlipidemia.
For your information this is very useful to you, it’s a summary of different lipidemias. (If you understand the previous lecture it’ll help you)

*One of the defects of dyslipidemias could be the enzymes or receptors.

*One of the enzymes that are known to be defected and cause dyslipidemias (specially chylomicronemia) is the lipoprotein lipase in the tissue that hydrolyses triglyceride into fatty acid and glycerol. So the defect in the lipoprotein lipase causes the chylomicrons triglyceride in VLDL not to be hydrolyzed and the chylomicrons will be in very high level in blood.

*Deficiency in lipoprotein lipase disorder shows that not one mutation happen to the enzyme but more than one (autosomal recessive).
How could you identify the mutations that cause defects in lipoprotein lipase to confirm the diagnosis of chylomicronemia or VLDL?!

-A student answer that by chirotpe (the looking at the morphology of the chromosome under the microscope) BUT the doctor said that this is not the correct answer.

-The correct is by the PCR (polymerase chain reaction), HOW?!

You could take the DNA of the patient and you synthesize primers around the gene of lipoprotein lipase, you know the sequence from this end to this end and you the PCR you amplify that piece of DNA that belongs to lipoprotein lipase gene and by using restriction fragment length polymorphism technique you could tell that this gene is defected and what type of mutation.

"يعني بنعمل اكتر من نسخة للDNA " وبنكتشف وين الخطأ في الجينات

-Another method is to use specific primer for specific mutation if there is a reaction between that primer with the amplifying DNA that will tell you that the mutation is there (we will talk about molecular diagnosis of genetic diseases Insha’Allah☺)
this condition characterized primarily by chylomicronemia (that rich in TG) so we measure the plasma TG

**Genetics**

Familial LPL deficiency is a rare, autosomal recessive condition that affects about one in one million children

Parents are often consanguineous.

Result from a variety of mutations in the LPL gene
Diagnosis

1- Measurement of plasma TG after 12 hour fasting.
2- Detection of chylomicron band by electrophoresis.
3- Test for post-heparin lipolytic activity (PHLA).
   LPL is attached to the surface of endothelial cells through a heparin-binding site. After the intravenous injection of heparin (60 units/kg), LPL is released and the activity of the enzyme is assessed in plasma drawn 45 min after the injection.
4- LPL released can also be assessed, using an ELISA assay.

what doctor say about 2:
we take blood sample & do biochemical reactions use enzymes & measure the concerned compounds by using spectrophotometer
take blood sample ==> centrifuging it ==> get plasma of the serum ==> take specific amount of serum of plasma ==> add specific chemical reagents in the presence of specific enzymes

example:
if you want to determine the amount of TG you take 0.1 mL serum and by using LPL the TG is hydrolyzed to FA & glycerol let glycerol to react with any other colored chemical that will give you a complex and by measuring the absorbance of spectrophotometer that will help you to determine how many milligram of TG per dL in the blood sample

: spectrophotometer
https://www.youtube.com/watch?v=pxC6F7bK8CU
How does a spectrophotometer work?

(الدكتور لم يشرحها وقال عليها سؤال او سؤالين):

https://www.youtube.com/watch?v=pxC6F7bK8CU
Indirect and Sandwich ELISA
Familial Hypercholesterolemia

- Autosomal dominant disorder.
- Due to mutation in the gene encoding the LDL receptor.
- LDL receptor, a cell surface protein, is responsible for binding to LDL and delivering it to the cell interior.
- It is an example for protein receptor disorder.
- It is the most frequent mendelian disorder.
- Both homozygotes and heterozygotes develop premature heart disease as a result of Atheromas (deposits of LDL-derived cholesterol in coronary arteries), Xanthomas (cholesterol deposits in skin and tendons) and Arcus cornea (deposits of cholesterol round the periphery of cornea).

<table>
<thead>
<tr>
<th>Plasma cholesterol levels in normal and familial hypercholesterolemic individuals.</th>
</tr>
</thead>
<tbody>
<tr>
<td>Normal</td>
</tr>
<tr>
<td>FH Heterozygote</td>
</tr>
<tr>
<td>FH Homozygote, genes of both parents are defected</td>
</tr>
</tbody>
</table>

Gene of LDL receptor is the defected gene.

Xanthoma
Diagnosis

• Measurement of plasma total cholesterol after 12 hour fasting.
• Detection of LDL (β-lipoprotein) band by electrophoresis.
• Direct DNA analysis of the molecular defect(s) of LDL receptor gene.

Case Report

A 2.5 months old boy born of third degree consanguineous marriage weighing 4.5kg attended to our OPD with the complaints of black tarry stool for last 3-4 days with pallor and gradual distension of abdomen. When blood was drawn for laboratory tests it appeared milky in colour (Fig:2). On examination baby was active, playful and multiple xanthomatosus eruption (Fig:1) seen over knees and extensor aspect of the limbs with moderate hepatosplenomegaly. Blood reports showed Hb 6.9gm/dl, TLC 13100/cumm, N50, L42, E5, M3, B0 Platelet count 1.38lacks/cumm, ESR 45mm, Reticulocyte count 2.8% with hypocromia and anisocytosis in peripheral blood smear.

Lipid profile report showed grossly lipemia- triglyceride (TG) 28980 mg/dl, total cholesterol 3820 mg/dl. Increased TG interferes the assay of other factors. Ophthalmoscopy showed lipemic retinitis. Lipid profile of mother was normal but father had increased Triglyceride (230mg/dl) and low HDL cholesterol (38mg/dl).

this case is : LPL deficiency

NOTES:
hepatomegaly & splenomegaly => because of infiltration of excess lipids
normal Hb is 12-15 and may reach 20 in infants

listen to record 32:25 if you want to know doctor notes
*doctor notes are very similar to what we wrote in the previous pages
AA is a 7-year-old boy delivered by spontaneous vaginal delivery in a primary health care center with uneventful pregnancy. While being investigated for jaundice in the 2nd day of life, he was discovered to have high cholesterol >500 mg/dL (>5.68 mmol/L, normal <4.40 mmol/L), low hemoglobin (HB) 6.7 g/dL (normal range 13.6–19.6 g/dL), and normal serum bilirubin and platelet count. The lipid profile was repeated. The laboratory work showed a very thick blood sample that was hyperlipidemic (Figure 1). The repeated lipid profile showed (laboratory method used: AEROSET system and ARCHITECT c8000 system) serum cholesterol 7.4 mmol/L (normal <4.40 mmol/L), high density lipoprotein (HDL) 1.10 mmol/L (normal >1.55 mmol/L), and triglyceride (TG) 80 mmol/L (normal <1.70 mmol/L). Based on this very abnormal lipid profile compared to his age, the primary healthcare facility started him on lipid lowering agents: gemfibrozil (lipoid) 300 mg twice a day and pravastatin 10 mg once a day. AA was referred to a tertiary hospital at age 60 days.
Further history revealed that AA is the first child born to first-degree consanguineous parents with positive family history of hyperlipidemia, maternal side in old age (father and aunt). There is no history of sudden death, premature cardiovascular disease, or recurrent pancreatitis in the family. Both parents had no history of hyperlipidemia.

Examination revealed an active child with no dysmorphic features or skin lesions. Abdominal examination revealed hepatomegaly. Cardiovascular examination was normal, as well as blood pressure. He was referred to the ophthalmologist for retinal examination which showed lipemis retinalis.

Laboratory investigation showed normal low-density lipoprotein (LDL), high-density lipoprotein (HDL), liver enzymes, baseline echocardiogram (ECHO), electrocardiogram (ECG), and ultrasound spleen. Ultrasound of abdomen confirmed hepatomegaly. Blood investigations are summarized in (Table 1).

<table>
<thead>
<tr>
<th>Lipid</th>
<th>2 months</th>
<th>18 months</th>
<th>2 years</th>
<th>4 years</th>
<th>Normal range</th>
</tr>
</thead>
<tbody>
<tr>
<td>CHO (mmol/L)</td>
<td>2.58</td>
<td>1.7</td>
<td>3.99</td>
<td>4.4</td>
<td>&lt;4.40</td>
</tr>
<tr>
<td>TG (mmol/L)</td>
<td>3.26</td>
<td>&gt;19</td>
<td>11.32</td>
<td>&gt;10.06</td>
<td>&lt;1.70</td>
</tr>
<tr>
<td>HDL (mmol/L)</td>
<td>0.6</td>
<td>0.6</td>
<td>0.45</td>
<td>0.37</td>
<td>&lt;1.55</td>
</tr>
<tr>
<td>LDL (mmol/L)</td>
<td>1.04</td>
<td>0.5</td>
<td>0.87</td>
<td>0.7</td>
<td>&lt;2.200</td>
</tr>
<tr>
<td>VLDL</td>
<td>N5</td>
<td>4.45</td>
<td>N5</td>
<td>N5</td>
<td>N5</td>
</tr>
<tr>
<td>LFT</td>
<td>232</td>
<td>339</td>
<td>359</td>
<td>345</td>
<td>&lt;500</td>
</tr>
<tr>
<td>ALK (u/L)</td>
<td>39</td>
<td>45</td>
<td>60–92</td>
<td>33</td>
<td>3–34</td>
</tr>
<tr>
<td>ALT (u/L)</td>
<td>21</td>
<td>18</td>
<td>14</td>
<td>15</td>
<td>5–55</td>
</tr>
<tr>
<td>GGT (u/L)</td>
<td>1</td>
<td>2</td>
<td>9</td>
<td>7</td>
<td>12–64</td>
</tr>
<tr>
<td>CBC</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Hb [g/dL]</td>
<td>10.5</td>
<td>12.4</td>
<td>11.0–14.5</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Hct [%]</td>
<td>0.287</td>
<td>0.287</td>
<td>0.340–0.440</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

THE END

good luck for all