Testing Facts: Apolipoprotein E

Description
Apolipoprotein E (apoE) is a multifunctional protein that plays a key role in lipoprotein metabolism and cardiovascular disease. The primary metabolic role of apoE is to transport cholesterol from the cells in the blood vessel wall to the liver for excretion. Two amino acid substitutions in the apoE structure result in three forms of apoE protein that differ in structure and function. These differences are associated with dissimilar disease risk and treatment outcomes. Incorporating a patient’s apoE genotype into diagnostic and treatment protocols may guide therapy and improve patient outcomes.

Functions of Apolipoprotein E
- ApoE is a constituent of triglyceride rich chylomicrons, VLDL and their remnants and HDL.
- The protein is involved in the efficient hepatic uptake of lipoprotein particles, stimulation of cholesterol efflux from macrophage foam cells in atherosclerotic lesions, and the regulation of immune and inflammatory responses.
- ApoE functions as a ligand for lipoprotein receptors and modulates lipoprotein levels by influencing the cholesterol clearance rate.
- Isoform specific variations (apoE 2, 3 or 4) include lipid and receptor binding differences that produce a difference in how lipids are metabolized.

Clinical Implications
- There is a linear relationship of apoE genotypes with LDLc and coronary risk:
  - 2/2, 2/3, 2/4, 3/3, 3/4, 4/4
- ApoE2 is associated with a 20% lower risk of CAD and apoE4 is associated with a slightly higher risk of CAD compared to apoE3.
- Lower plasma levels of apoE inhibit normal lipid metabolism.
- ApoE4 individuals have greater intestinal absorption and delayed clearance of cholesterol leading to elevated LDLc and apoB levels.
- ApoE2 individuals may have weaker LDL receptor binding capacity which delays clearance of VLDL and remnants in the plasma.
- ApoE 2/2 genotype is associated with the genetic disorder type III hyperlipidemia and the risk of premature cardiovascular disease.
- ApoE genotype is a genetically fixed characteristic. It need only be determined once.

Treatment Implications

Lifestyle
- ApoE4 individuals may have significantly greater LDLc reduction in response to low fat diet than those with apoE3/3 genotype.
- The potential for an apoE2/2 to develop type III hyperlipidemia is largely dependent on environmental issues such as body fat and diets high in simple carbohydrates.
- ApoE3 or apoE2 individuals may have more favorable changes in lipids from exercise compared to apoE4 individuals.

Pharmacologic Implications
- ApoE4 individuals may have less LDLc reduction on statin therapy than apoE3s or E2s, but have equivalent CAD risk reduction.
- The LDLc response to omega-3 fish oil may be dose dependent in apoE4s.
## Testing Facts: Apolipoprotein E

### Apolipoprotein E Gene-Environment Interactions

<table>
<thead>
<tr>
<th>ApoE Isoform</th>
<th>ApoE2</th>
<th>ApoE3</th>
<th>ApoE4</th>
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<tbody>
<tr>
<td>Frequency</td>
<td>1,2,3,4</td>
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<td>CVD Risk</td>
<td>1,2,3,4</td>
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<td>Plasma apoE levels</td>
<td>5,6</td>
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<td>Binding properties</td>
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<tr>
<td>Mechanisms effecting lipid levels</td>
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<tr>
<td>Lipid levels differences compared to apoE 3/3</td>
<td>1,2,5,7,8</td>
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<tr>
<td>Response to low-fat diet &lt; 30%</td>
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<td>Response to statins</td>
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<td>Response to omega-3 fish oil</td>
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<td>Response to moderate alcohol</td>
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<td>Increased risk for carotid atherosclerosis due to smoking</td>
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<td>Response to exercise training</td>
<td>5,15</td>
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### References: