Domain II: Nutritional Biochemistry (12% of Exam)

Case Study Applications

Case Study 1: Impaired Glucose Metabolism and Mitochondrial Function

Case Overview

A 42-year-old male presents with post-meal fatigue, mild dyslipidemia, and fasting glucose of 105 mg/dL. He reports high caffeine intake, limited exercise, and frequently skipped meals. Organic acid testing shows elevated lactate and low citrate, suggesting incomplete glucose oxidation and impaired TCA cycle activity.

Connection to Domain II

This case highlights the integration of **carbohydrate metabolism and mitochondrial energy production**, emphasizing the biochemical pathways of glycolysis, pyruvate oxidation, and the citric acid cycle. It reflects **Domain II competencies** in energy metabolism, cofactor biochemistry, and oxidative stress regulation.

Functional Lab Markers to Consider

- Organic acids (lactate, pyruvate, citrate, succinate)
- Fasting glucose, insulin, and HbA1c
- Serum B1, B2, B3, B5, and alpha-lipoic acid levels
- Comprehensive Metabolic Panel (AST, ALT, ALP)
- hs-CRP and homocysteine (oxidative stress and inflammation markers)

Key Learning Concepts

- Pyruvate dehydrogenase (PDH) is the critical enzyme linking glycolysis to the TCA cycle, requiring thiamine, lipoic acid, riboflavin, niacin, and pantothenic acid.
- Thiamine deficiency shifts pyruvate toward lactate formation, decreasing acetyl-CoA availability.

- Chronic stress, caffeine, and inconsistent eating patterns can exacerbate mitochondrial inefficiency.
- Energy deficit and oxidative stress impair glucose tolerance and increase fatigue.

CNS Sample Questions

1. Which nutrient deficiency most likely contributes to this client's elevated lactate and fatigue?
A. Riboflavin
B. Thiamine
C. Biotin
D. Vitamin C
Correct Answer: B. Thiamine
Rationale: Thiamine is a cofactor for PDH, the enzyme converting pyruvate to acetyl-CoA. Deficiency increases lactate accumulation due to impaired oxidative metabolism.

2. Which cofactor supports the conversion of succinate to fumarate in the TCA cycle?
A. Niacin
B. Riboflavin
C. Pantothenic acid
D. Thiamine
Correct Answer: B. Riboflavin
Rationale: Riboflavin (as FAD) is required by succinate dehydrogenase, an enzyme in both the TCA cycle and electron transport chain.

3. Which laboratory finding supports mitochondrial dysfunction secondary to B-vitamin deficiency?
A. Elevated triglycerides
B. Low ALT and AST
C. Elevated lactate and low citrate
D. Elevated uric acid
Correct Answer: C. Elevated lactate and low citrate
Rationale: This pattern reflects impaired oxidative metabolism and reduced TCA cycle flux, common in B-vitamin insufficiency.

Case Study 2: Dysregulated Lipid Metabolism and Inflammation

Case Overview

A 55-year-old woman with metabolic syndrome presents with elevated triglycerides (220 mg/dL), low HDL (38 mg/dL), and high hs-CRP (5.4 mg/L). A fatty acid profile shows an omega-6 to omega-3 ratio of 15:1, indicating an inflammatory lipid environment.

Connection to Domain II

This case integrates **lipid metabolism, cytokine and eicosanoid pathways**, and the biochemical role of fatty acids in inflammation. It aligns with **Domain II competencies** in lipid oxidation, prostaglandin synthesis, and enzyme cofactor chemistry.

Functional Lab Markers to Consider

- Fatty acid profile (AA/EPA ratio, omega-3 index)
- Fasting insulin and glucose
- ApoB, ApoA1, and triglycerides
- hs-CRP and fibrinogen (inflammatory markers)
- Liver enzymes (ALT, AST, GGT)

Key Learning Concepts

- Linoleic acid (omega-6) is converted to arachidonic acid, the substrate for pro-inflammatory prostaglandins (PGE2) and leukotrienes (LTB4).
- EPA and DHA (omega-3s) produce anti-inflammatory eicosanoids (PGE3, resolvins).
- High omega-6:omega-3 ratios favor COX-mediated PGE2 synthesis and cytokine activation.
- Zinc, magnesium, and B6 are required cofactors for fatty acid desaturase enzymes.
- Dysregulated lipid metabolism contributes to endothelial inflammation and insulin resistance.

CNS Sample Questions

1. Which eicosanoid predominates with a high omega-6 intake and contributes to inflammation?
A. PGE3
B. PGI3
C. PGE2
D. LTB5
Correct Answer: C. PGE2
Rationale: PGE2, derived from arachidonic acid, is a pro-inflammatory mediator that increases pain and vascular permeability.

2. Which nutrient directly supports delta-6-desaturase activity for PUFA metabolism?
A. Zinc
B. Selenium

C. Iron
D. Vitamin C
Correct Answer: A. Zinc
Rationale: Zinc is a cofactor for delta-6-desaturase, the enzyme required to convert linoleic acid to gamma-linolenic acid.

3. Which dietary intervention best supports a balanced eicosanoid profile?
A. Reduce omega-3 intake and increase saturated fat
B. Increase omega-3 intake and reduce processed seed oils
C. Eliminate all fats from the diet
D. Increase trans-fat consumption to reduce inflammation
Correct Answer: B. Increase omega-3 intake and reduce processed seed oils
Rationale: Shifting the omega-6:omega-3 ratio toward anti-inflammatory prostaglandin synthesis lowers systemic inflammation.

Case Study 3: Methylation and Epigenetic Regulation

Case Overview

A 40-year-old female presents with fatigue, anxiety, and a family history of cardiovascular disease. Genetic testing reveals an MTHFR C677T variant, and serum homocysteine is 16 μmol/L. Her diet is low in leafy greens and animal protein. She reports using oral contraceptives for 10 years.

Connection to Domain II

This case highlights **methyl donor biochemistry, nutrient-gene interactions, and one-carbon metabolism**, key areas of **Domain II**. It illustrates how nutrient status, genetics, and biochemistry intersect to regulate epigenetic expression and disease risk.

Functional Lab Markers to Consider

- Homocysteine, SAM/SAH ratio
- RBC folate, serum B12, B6, and riboflavin
- Methylmalonic acid (B12 functional marker)
- Serum zinc
- Genetic testing for MTHFR and COMT variants

Key Learning Concepts

- MTHFR polymorphisms reduce conversion of 5,10-methylene THF to 5-MTHF, impairing homocysteine remethylation.

- Elevated homocysteine increases oxidative stress, endothelial dysfunction, and DNA hypomethylation.
- Active methyl donors include 5-MTHF, methylcobalamin, betaine, and SAMe.
- Oral contraceptives can deplete B-vitamins involved in methylation.
- Epigenetic modification (methylation of DNA and histones) regulates gene expression and stress resilience.

CNS Sample Questions

1. Which nutrient form best bypasses reduced MTHFR activity?
A. Folic acid
B. 5-MTHF
C. Folinic acid
D. PABA
Correct Answer: B. 5-MTHF
Rationale: 5-methyltetrahydrofolate is the active, methylated form of folate that can directly participate in homocysteine remethylation, bypassing MTHFR enzyme limitations.

2. Which enzyme requires both zinc and vitamin B6 in the transsulfuration pathway?
A. Methionine synthase
B. Cystathionine beta-synthase
C. MTHFR
D. COMT
Correct Answer: B. Cystathionine beta-synthase
Rationale: This enzyme converts homocysteine to cystathionine and requires pyridoxal-5-phosphate (B6) and zinc as cofactors.

3. Which biochemical imbalance would most likely occur with this client's presentation?
A. Elevated SAM/SAH ratio and hypermethylation
B. Low homocysteine and low methylation potential
C. Elevated homocysteine and hypomethylation
D. Elevated cysteine and increased glutathione
Correct Answer: C. Elevated homocysteine and hypomethylation
Rationale: MTHFR variants reduce folate recycling, leading to homocysteine accumulation and reduced methyl group availability.

Case Study 4: Oxidative Stress Across the Life Cycle

Case Overview

A 68-year-old woman reports fatigue, memory decline, and muscle weakness. She takes a statin for high cholesterol. Labs show elevated homocysteine, low CoQ10, and borderline low vitamin E.

Connection to Domain II

This case connects **oxidative stress, mitochondrial function, and nutrient-drug interactions**—core biochemical themes within **Domain II**. It emphasizes redox balance, antioxidant regeneration, and nutrient involvement in the electron transport chain.

Functional Lab Markers to Consider

- CoQ10 (plasma or RBC)
- Homocysteine
- Lipid peroxides (oxidative damage marker)
- Vitamin E, vitamin C, selenium
- RBC glutathione and total antioxidant capacity

Key Learning Concepts

- CoQ10 serves as an electron carrier in the mitochondrial respiratory chain, supporting ATP synthesis and antioxidant protection.
- Statins inhibit HMG-CoA reductase, reducing endogenous CoQ10 synthesis.
- Aging reduces mitochondrial density and increases oxidative stress.
- Vitamin E protects lipid membranes from peroxidation; vitamin C regenerates oxidized vitamin E.
- Elevated homocysteine increases oxidative load and cardiovascular risk.

CNS Sample Questions

1. Statins may cause fatigue by reducing which compound in the electron transport chain?
A. NADH
B. CoQ10
C. FADH2
D. Carnitine
Correct Answer: B. CoQ10
Rationale: Statins block HMG-CoA reductase, reducing CoQ10 synthesis and impairing mitochondrial ATP production.

2. Which antioxidant regenerates oxidized vitamin E?
A. Vitamin C
B. Selenium
C. Zinc

D. Glutamine
Correct Answer: A. Vitamin C
Rationale: Vitamin C donates electrons to regenerate reduced, active vitamin E, maintaining antioxidant capacity in lipid membranes.

3. Which combination of nutrient supplementation best supports redox balance in this case?
A. Zinc and vitamin B6
B. CoQ10 and vitamin C
C. Calcium and phosphorus
D. Iron and vitamin K
Correct Answer: B. CoQ10 and vitamin C
Rationale: CoQ10 supports mitochondrial ATP production, while vitamin C enhances antioxidant recycling and mitigates oxidative stress.