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CASE REPORT

The Role of Fat Soluble Vitamins in Clinical Lipidology

Lauren Williams[1*], Catherine McNeal[2] and Don P Wilson[1]

[1]*Pediatric Endocrinology and Diabetes, Cook Children's Medical Center, USA*

[2]*Department of Pediatrics and Internal Medicine, Division of Cardiology, Baylor Scott & White Healthcare Temple, USA*

***Corresponding author:** *Lauren Williams, RD, Pediatric Endocrinology and Diabetes, Cook Children's Medical Center, Fort Worth, TX, USA, E-mail: lauren.williams@cookchildrens.org*

Abstract

Fat Soluble Vitamins (FSV) is essential for the normal growth and development of children. Many genetic and acquired conditions have the potential of interfering with FSV absorption and transport. Understanding the physiology of these conditions is imperative in providing effective treatment, including prevention of FSV deficiency. In this article, we present three case studies that illustrate the importance of FSVs. We explore recommended intake of each of the FSV as well as clinical signs of deficiency. Further discussion and research is needed to improve awareness of FSV deficiency by clinical lipidologists, the prevalence of FSV deficiency in these disorders, and effective strategies for effective treatment and prevention.

Keywords

Fat-soluble vitamins, Lipidology, Lipoproteins, Metabolism

Introduction

Clinical lipidologists encounter a variety of genetic and acquired conditions that alter lipid and lipoprotein metabolism. Effective treatment requires accurate diagnosis and understanding of the disease process. Dietary fat and lipoproteins play an important role in the normal absorption and transport of Fat Soluble Vitamins (FSV), which are essential for health and wellness, including normal growth and development in young children. In this article we discuss a variety of conditions and interventions which may disrupt FSV absorption and transport, resulting in well described clinical manifestations of deficiency (Figure 1).

Case #1

A 15-year-old boy developed progressive dementia and an abnormal gait. His birth and development were normal, except for intractable diarrhea during childhood. Xanthomas were recognized at 7 years of age; cataracts at age 10 [1]. His total plasma cholesterol, LDL cholesterol, and triglycerides were normal.

Case #2

A previously healthy, developmentally normal 3-year-old boy developed Xanthomas of the extensor surfaces of the elbows and knees. His stools were very pale in color, and he had begun complaining of pruritus and abdominal discomfort, which caused a decrease in his appetite. Mild scleral icterus was noted. A fasting lipid profile revealed elevations in total cholesterol (1184 mg/dL) and Low-Density Lipoprotein Cholesterol (LDL-C, 510 mg/dL). Triglycerides were within normal limits (47 mg/dL). Liver tests were markedly abnormal [2].

Case #3

A 2-month-old female was noted to have lipemic serum during a routine blood draw. Plasma triglycerides were > 2000 mg/dL, which was confirmed upon repeat testing. She was continued exclusively on breastfeeding. At 6 months of age, the child presented to an emergency department after 24 hours of refusing feedings, irritability, low-grade fever, and 2 episodes of non bilious vomiting. On physical examination, her abdomen was distended and tender to palpation. Eruptive Xanthomas were noted over the buttocks. The child's body fat distribution was normal. These 3 cases help illustrate the potential disruption in FSV absorption transport either as a consequence of the underlying disorder, medical interventions used to treat them, or both.

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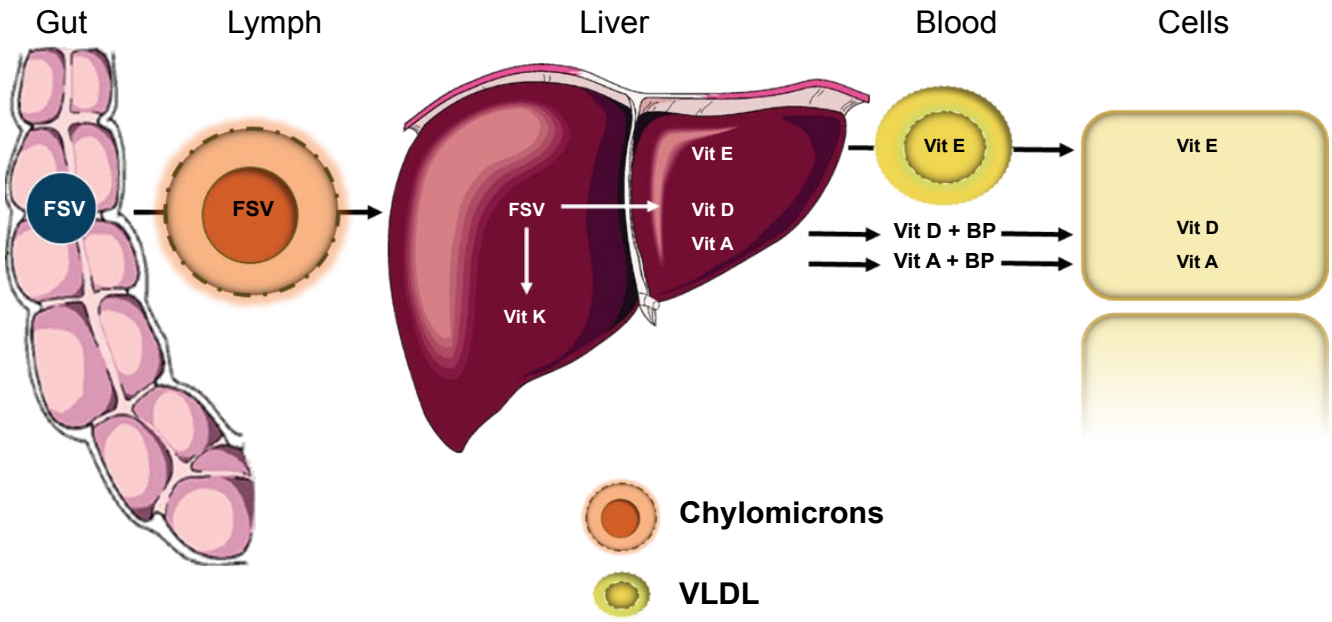

Figure 1: FSV absorption and transport.

Following hydrolysis, FSV (Vitamins A, E, D and K, as well as carotenoids), are captured from mixed micelle by the apical membrane transporters, including Scavenger Receptor class B1 (SR-B1), Cluster Determinant 36 (CD36) and Niemann-Pick C1-Like1 (NPC1L1). Although incompletely understood, it is thought that proteins are involved in transport of FSV and carotenoids within the enterocyte. Non-metabolized vitamins and carotenoids are incorporated into chylomicrons and secreted into the lymph. Following transport to the liver, FSV are either metabolized, stored or transported to target cells via VLDL and binding proteins.

Table 1: Comparison of water-versus fat-soluble vitamins.

	Water soluble vitamins	**Fat-soluble vitamins**
Vitamins	B, C	A, D, E, K
Site of Absorption	Small intestines	Small intestine
Dietary Intake	Excess intake usually detected and excreted by the kidneys	Excess intake tends to be stored in fat-storage sites
Solubility	Hydrophilic	Hydrophobic
Capitalize	Easily absorbed the blood, travels freely in the bloodstream	Absorbed into the lymphatic system, many require protein carriers to travel in the blood
Body storage	Not generally	Yes
Deficiency	Deficiency symptoms appear relatively quickly	Deficiency symptoms are slow to develop
Toxicity	Low risk	Higher risk
Need for daily consumption	Yes	No

Case #1: Cerebrotendinous Xanthomatosis [CTX] is a rare disease characterized by the accumulation of cholesterol and cholestanol in brain and tendons. It is caused by a mutation in the sterol 27-hydroxylase gene [CYP27A1] involved in bile acid synthesis. Disruption of bile salts, such as in this case, also impairs FSV absorption. Cataracts become evident in childhood or adolescence, and xanthomata develop in the 2nd and 3rd decades of life. Significant neurologic impairment also occurs; this often includes seizures, dementia, and extra pyramidal dysfunction, typically beginning in the 3rd decade of life and progresses until death [3].

Case #2: Although this child's clinical presentation (Xanthomas with marked elevation of total and LDL cholesterol) suggests the possibility of familial hyper cholesterolemia, his clinical, laboratory, and liver biopsy findings were consistent with familial sclerosing cholangitis [2]. The liver plays a key role in fat and FSV absorption and metabolism. It synthesizes bile salts, which facilitate emulsification of dietary fat and activate lipases, which aid in hydrolysis of fats. Inherited or acquired liver diseases can present with profound changes in the plasma concentration of lipids and lipoproteins, and malabsorption of FSV.

Case #3: Familial Chylomicronemia Syndrome (FCS) is an autosomal recessive disorder characterized by severe hypertriglyceridemia, with triglyceride levels generally > 1000 mg/dL. Because the severe hypertriglyceridemia in FCS is the result of dietary derived chylomicrons, standard lipid lowering therapies, such as omega-3-fatty acids, niacin, and fibrates, are generally ineffective [4]. Triglycerides may be substantially lowered, however, by restricting dietary fat to < 10-15% of the total daily caloric intake [5]. If triglycerides are not

Table 2: Micronutrient Dietary Reference Intakes (DRIs): Recommended dietary allowances and adequate intakes, fat soluble vitamins.

Age	Vitamin A (µg/d)	Vitamin D (µg/d)	Vitamin E (mg/d)	Vitamin K (µg/d)
Infants				
0-6 months	**400***	10*	**4***	2.0*
7-12 months	**500***	10*	**5***	2.5*
Children				
1-3 years	**300**	15	**6**	30*
4-8 years	**400**	15	**7**	55*
Males				
9-13 years	**600**	15	**11**	60*
14-18 years	**900**	15	**15**	75*
19-70 years	**900**	15	**15**	120*
> 70 years	**900**	20	**15**	120*
Females				
9-13 years	**600**	15	**11**	60*
14-18 years	**700**	15	**15**	75*
19-50 years	**700**	15	**15**	90*
51-70 years	**700**	15	**15**	90*
> 70 years	**700**	20	**15**	90*
Pregnancy				
14-18 years	**750**	15	**15**	75*

Note: Table depicts Recommended Dietary Allowances (RDAs) in bold and Adequate Intakes (AIs) followed by an asterisk (*). Table modified from: Texas Children's Hospital Pediatric Nutrition Reference Guide [8].

Table 3: FSV sources and clinical signs of deficiency [9].

	Examples of dietary sources	Phenotypic signs of deficiency
Vitamin A	Sweet potato, Raw carrots, Red bell pepper, Spinach, Butternut squash, Cantaloupe	Xerophthalmia, Follicular hyperkeratosis, Impaired immunocompetence
Vitamin D	Cod liver oil, Sockeye salmon, Fortified cow's milk, Sardines, Egg yolk, Liver	Rickets, Osteomalacia
Vitamin E	Almonds, Sunflower oil, Mixed nuts, Canola oil, Asparagus, Olive oil, Spinach	Poor transmission of nerve impulses, Muscle weakness, Retinal degeneration
Vitamin K	Collard greens, Kale, Spinach, Broccoli, Asparagus, Avocado, Carrots	Hypoprothrombinemia, Hemorrhage

lowered to goal, further dietary fat restriction may be necessary while ensuring daily essential fat intake (2-4% daily caloric intake from linoleic acid and α-linolenic acid) [6,7]. Such severe restriction of dietary fat as well as impaired long chain fat metabolism, however, may also result in FSV deficiency.

Discussion

Vitamins are organic compounds necessary for normal growth and maintenance of good health. They are generally classified as being water- or fat-soluble. Important differences exist between water and fat-soluble vitamins (Table 1). Micronutrient Dietary Reference Intakes (DRIs): Recommended Dietary Allowances and Adequate Intakes, Fat Soluble Vitamins and Calcium are listed in Table 2.

Although available as dietary supplements, in most humans, FSV are obtained from food sources. Following ingestion, FSV require bile for digestion and absorption. FSV are soluble in lipids, but not in aqueous solutions. Therefore, once absorbed FSV are incorporated into chylomicrons and transported by the lymphatic system. Vitamins A, D and E accumulate in the liver and fat tissue, and are not readily excreted. As a result, excessive intake can result in toxicity, particularly for vitamins A and D. Due to this, care should be taken to supplement only when necessary to avoid excessive intake. In contrast, vitamin K is easily excreted by the body. Dietary sources of FSV as well as signs of deficiency are included in Table 3.

Table 4 lists lipid and lipoprotein disorders that potentially disrupt FSV absorption and metabolism. In addition, a variety of medications that interfere with intestinal absorption of fats (bile acid resins) or interrupt chylomicron and VLDL production and release, such as antisense apoB therapy and MTP inhibitors, may cause FSV deficiency.

Patients with disorders that disrupt FSV absorption and metabolism may benefit from routine monitoring of FSV levels with appropriate supplementation as needed for indicated deficiencies. Further research is needed on this topic to determine incidence of FSV deficiency in these conditions as well as most effective protocols for supplementation.

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Table 4: Lipid disorders and medications that disrupt fat soluble vitamin absorption/metabolism.

Condition	Description	Lipid abnormality	Inheritance	Mutation	Testing	Clinical manifestations
Abetalipoproteinemia	Disrupts intracellular lipid transport in the intestine (chylomicrons) and liver (VLDL)	Absence of LDL and Very Low-Density Lipoprotein (VLDL)	Autosomal recessive	Microsomal Triglyceride Transfer Protein (MTP)	Lipid panel. Genetic testing available.	Affected infants may appear normal at birth, but by the first month of life, they develop steatorrhea, abdominal distention, and growth failure. Children develop retinitis pigmentosa and progressive ataxia, with death usually occurring by the third decade.
Familial hypobetalipoproteinemia	Abnormal apolipoprotein B	Low LDL	Autosomal codominant	apoB	Lipid panel, apoB. Genetic testing available.	Homozygotes present with fat malabsorption and low plasma cholesterol levels at a young age. They develop progressive neurologic degenerative disease, retinitis pigmentosa, and acanthocytosis, similar to patients with ABL.
Chylomicron retention disease	Impaired transport of chylomicrons within enterocytes	Lack of chylomicrons	Autosomal recessive	SAR1B	Postprandial lipid panel. Genetic testing available.	Failure to thrive; diarrhea; and steatorrhea. Other features of this disorder may develop later in childhood and often impair the function of the nervous system.
Smith-Limli-Opitz syndrome	Severe defect in cholesterol biosynthesis	Low LDL	Autosomal recessive	7-Dehydrocholesterol Reductase (DHCR7)	Elevated levels of the cholesterol precursor 7-dehydrocholesterol. Genetic testing available.	Growth failure; moderate-to-severe mental deficiency with variably altered muscle tone and dysmorphic features. Despite severe deficiency of normal bile acids, fat malabsorption and deficiencies of fat soluble vitamins are not common.
Lysosomal Acid Lipase Deficiency (LAL-D)	Lysosomal storage disorder	Elevated LDL-C and triglyceride, Decreased HDL-C	Autosomal recessive	LIPA	Enzymatic blood test for lysosomal acid lipase. Genetic testing available.	Hepatomegaly, hepatic steatosis, accelerated atherosclerosis, corneal arcus, xanthomas. Liver disease may progress to liver failure.
Cerebrotendinous xanthomatosis (CTX)	Disruption of bile acid production	Normal-to-low plasma cholesterol concentration	Autosomal recessive	CYP27A1	Elevated plasma and tissue levels of cholestanol. Genetic testing available.	Infantile-onset diarrhea, childhood-onset cataract, tendon xanthomas, and progressive neurologic dysfunction.

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