

# PXE Awareness

*National Association for Pseudoxanthoma Elasticum  
(NAPE, Inc.)*

Volume 14, Issue 3, October 2008

# **ABCC6 and VITAMIN K K-2 ?**

# **National Association for Pseudoxanthoma Elasticum (NAPE, Inc.)**

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# President's Message

Dear NAPE Colleagues,

Lovely blue skies; crisp, cool fall air; a beautiful new hotel staffed by genial, helpful, capable personnel; an excellent restaurant. What more could we ask for our NAPE annual meeting! That is exactly what we found in Salt Lake City, a lovely, remarkably attractive and clean city. Our conference was a bit smaller than we have enjoyed in recent years thanks to our schedule, health issues and the economy which kept some from traveling. Nonetheless, we had a cohesive group of PXE patients, family members and marvelous doctors who focused with us on issues of great relevance for coping with PXE.

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This year much attention centered on research reporting PXE to be a metabolic disorder. Dr. Berthold Struk provided an excellent introduction to what is currently known in this area and implications stemming from it. Much interest was expressed in the possibility for treatments. In the meantime, we discussed nutritional strategies that might prove helpful. This issue features Dr. Struk's presentation with suggestions we may wish to implement in the knowledge that this is simply the beginning and that much remains to be discovered. NAPE will follow the research and continue to report findings through the newsletter.

Dr. Kattesh Katti and his colleague, Dr. Ravi Shukla, presented their findings in the research NAPE partially funded last year. Their conclusions and plans for the coming year will be featured in the next issue of *PXE Awareness*. Results to date are exciting, pointing to promise for the administration of medications through the use of nanotechnology. Our readers will appreciate a recent honor bestowed on Dr. Katti who has been named one of the world's 25 2008 most influential scientists in his research area. This is wonderful recognition for Dr. Katti whose nano discoveries are making a difference in a number of medical and technical fields. Congratulations, Dr. Katti, for yet another outstanding achievement.

NAPE is extraordinarily fortunate to have the support of Dr. Berthold Struk, surely the world's leading cardiology expert in PXE, and now Dr. Katti who has joined with enthusiasm in our search for improving treatments for those who suffer from retinal disorders. Both of these men not only are remarkably effective research scientists, but they also display the ability and desire to help individual patients deal with medical



problems. Their skill in communicating with lay persons made our 2008 conference most rewarding. Much time was given to sharing information about patient concerns, understanding those concerns and learning strategies for dealing with them. Participant evaluations noted the humanity of these caring men. Thank you, gentlemen, for helping NAPE fulfill its mission to provide education and support for PXE affected persons. We are deeply grateful for the commitment you bring to our cause, especially so since we know that your professional lives are intensely demanding. In the spiritual sense, you truly are the salt of the Earth!



With warm regards to all for a wonderful fall season from our NAPE office.

Fran Benham

Fran at Temple Square



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Drs. Katti, Benham, Struk, Shukla





# Pseudoxanthoma Elasticum: Are Vitamin K, Its Precursors and Metabolites the New Kids on the Block?

-Berthold Struk, MD, PhD

## Evidence from ABCC6 (-/-) Mice

- Tissue calcification in PXE results from loss of function of ABCC6 in the liver
- The phenotype can be rescued by transplantation of normal liver cells (from wild type mice) into the knockout mouse

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### Metabolic Disease Hypothesis

- Tissue calcification is due to the absence of a plasma factor secreted from the basolateral hepatocyte membrane due to loss of function of ABCC6
- The missing plasma factor could be vitamin K, a vitamin K precursor or a vitamin K metabolite
  - since vitamin K is an important co-factor for the gamma-carboxylation of gla-proteins, that in the carboxylated form prevent tissue calcification

### GLA-Proteins

- prevent tissue calcification
  - if they are carboxylated
- GLA-proteins are the



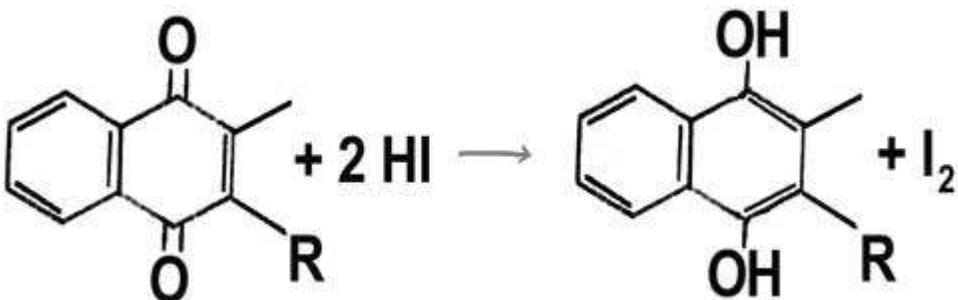
- Vitamin K-dependent clotting factors II, VII, IX and X (liver)
- osteocalcin
- matrix gla-protein (MGP)

## Matrix GLA-Protein

- excretion by vascular smooth muscle cells (VSMC)
- it is poorly soluble and remains close to VSMC
- associated with liver derived alpha-fetuin

## History of K-Vitamins

- The chemical substance class of “quinones”
  - was known since at least 1910
- chemically quinones were characterized and tested for
  - their ability to oxidize iodide to iodine
  - iodometric determination
- Iodometric determination
  - was used for the determination of the content of quinones in different
    - \* animal tissues
    - \* foods
- Iodometric determination



quinone + hydriodic acid → reduced quinone + iodine

I<sub>2</sub> (Iodine) + Starch → Blue Color

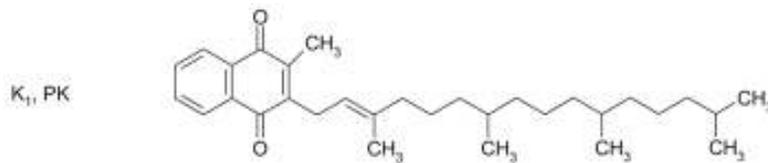


- 1945 Weston Price described a new vitamin-like activator

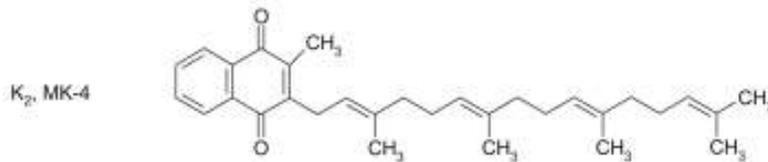
- influential on utilizing minerals,
- protecting against tooth decay,
- protecting against heart disease
- important for growth, development, reproduction and function of the brain

### Chemical Structure of Vitamin K Precursors and Metabolites

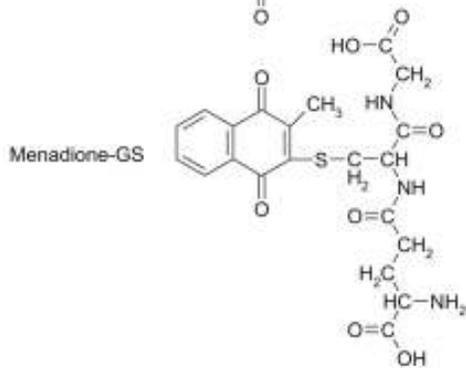
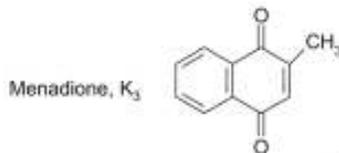
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natural form,  
Vitamin K1  
phylloquinone



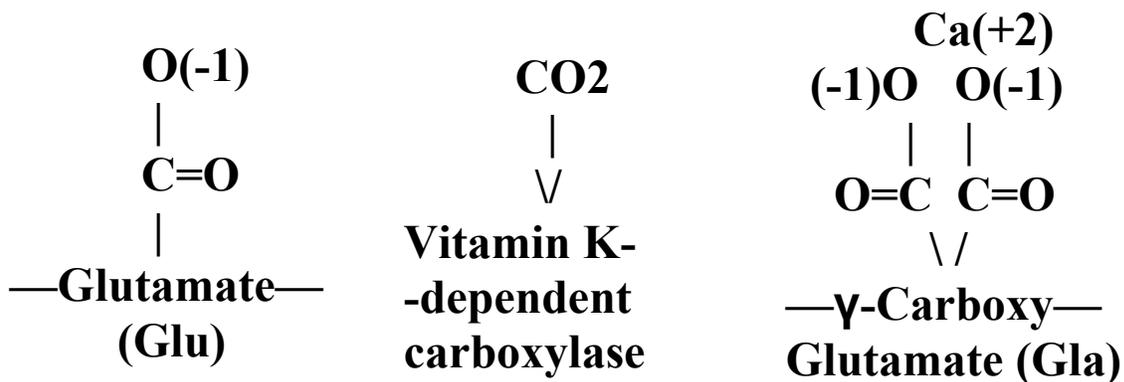
natural form,  
Vitamin K2  
menaquinone



## Vitamin K dependent carboxylation of GLA-proteins



- the Vitamin K-dependent gamma-glutamyl carboxylase (GGCX)
  - rearranges the chemical bonds within carbon dioxide by creating a **carboxyl** group
  - adds such carboxyl group as **second** group to the side chain of the amino acid glutamate and transforms it into  $\chi$ -**carboxy**glutamate
- The process is called  $\chi$ -**carboxylation**



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## Natural Sources of K-Vitamins

- butterfat
- organs and fat of animals consuming rapidly growing green grasses
- sea foods such as fish eggs
- fermented food (hard cheeses, sauerkraut, natto)





**Vitamin K2 Content of Selected Foods**  
(micrograms per 100 gram serving)

<b>FOOD</b>	<b>VITAMIN K2</b>	<b>(µg/100g)</b>
Natto	1103.4	(0% MK-4)
Goose Liver Paste	369.0	(100% MK-4)
Hard Cheeses	76.3	(6% MK-4)
Soft Cheeses	56.5	(6.5% MK-4)
Egg Yolk (Netherlands)	32.1	(98% MK-4)
Goose Leg	31.0	(100% MK-4)
Curd Cheeses	24.8	(1.6% MK-4)
Egg Yolk (United States)	15.5	(100% MK-4)
Butter	15.0	(100% MK-4)
Chicken Liver	14.1	(100% MK-4)
Salami	9.0	(100% MK-4)
Chicken Breast	8.9	(100% MK-4)
Chicken Leg	8.5	(100% MK-4)
Ground Beef (Medium Fat)	8.1	(100% MK-4)
Bacon	5.6	(100% MK-4)
Calf Liver	5.0	(100% MK-4)
Sauerkraut	4.8	(8% MK-4)
Whole Milk	1.0	(100% MK-4)
2% Milk	0.5	(100% MK-4)
Salmon	0.5	(100% MK-4)
Mackerel	0.4	(100% MK-4)
Egg White	0.4	(100% MK-4)
Skim Milk	0.0	
Fat-Free Meats	0.0	

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## What is Natto?



- Nattō (なっとう or 納豆?) is a traditional Japanese food made from fermented soybeans, popular especially for breakfast
- As a rich source of protein, nattō and the soybean paste miso formed a vital source of nutrition in feudal Japan
- For some, nattō can be an acquired taste due to its powerful smell, strong flavor and sticky consistency
- In Japan nattō is most popular in the eastern regions, including Kantō, Tōhoku, and Hokkaido.



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- Nattō is made from soybeans, typically a special type called nattō soybeans.
  - Smaller beans are preferred, as the fermentation process will be able to reach the center of the bean more easily.
  - The beans are washed and soaked in water for 12 to 20 hours. This increases the size of the beans.
  - Next, the soybeans are steamed for 6 hours, although a pressure cooker can be used to reduce the time.
  - The beans are mixed with the bacterium *Bacillus subtilis natto*, known as nattō-kin in Japanese.



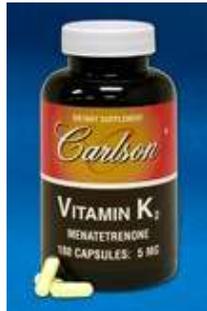
- From this point on, care has to be taken to keep the ingredients away from impurities and other bacteria.
- The mixture is fermented at 40°C for up to 24 hours. Afterwards the natto is cooled, then aged in a refrigerator for up to one week to add stringiness. During the aging process at a temperature of about 0°C, the Bacilli develop spores, and enzymatic peptidases break down the soybean protein into its constituent amino acids.

## Vitamin K2 Supplements (ASK YOUR PHYSICIAN FIRST!)

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Menatetrenone

Menaquinone – 4



Supplement Facts		
Serving Size 1 Capsule		
	Amount Per Capsule	% Daily Value
Vitamin K <sub>2</sub> (as menatetrenone)	5 mg	6250%

Menaquinone-7



Supplement Facts		
Serving Size 1 Softgel		
	Amount Per Softgel	% DV
MK-7 (Vitamin K <sub>2</sub> as Menaquinone-7) (from 60 mg Natto Extract)	90 mcg	112%
* Daily Value not established.		

\* \* \* \* \*

Editor's Note – Dr. Struk urges NAPE readers to tap into and read more about Vitamin K at the following website which provides much useful detail:

<http://www.westonaprice.org/basicnutrition/vitamin-k2>

# American Vitamin K2 Food Sources



- Fran Benham

Vitamin K, once referred to as “factor x,” yielded its secrets slowly over the last century. Once thought of simply as the blood clotting factor, today we recognize it as a complex, multi-faceted family of nutrients serving a variety of biological functions. Recent research revealed that while the normal aging process includes some calcification of elastic tissues, those who consume an adequate level of Vitamin K suffer less from this aging process. This finding led PXE researchers to hypothesize that Vitamin K might be implicated in the early elastic tissue calcification found in PXE patients. Recent studies, as indicated in the July 2008 issue of *PXE Awareness*, have confirmed this hypothesis. One study demonstrated that a PXE knockout mouse, treated with a normal liver tissue transplant, was able to process Vitamin K in a normal manner. While this excites hope, it is important to understand that much more complex human livers need much more study to possibly take this step.

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In the meantime, PXE patients want to know if they can do anything with this new information. Our doctors say yes, but proceed with caution. Do not over-indulge in Vitamin K consumption. Vitamin K1 is easy to find in the American diet – and we don’t need much. This issue includes a list of Vitamin K food sources along with amounts needed in normal diets. Our best advice is to consume the recommended amount – AND NO MORE. We need more data to do anything else.

Vitamin K2 is also very important, but we need much more information to be certain about amounts. Available research indicates that we do not need much K2. Our doctors tell us to consume it in small amounts for now. Those who decide to eat natto should do so no more often than once per week. Natto is not appealing to American tastes, but is by far the richest source of K2 in the diet. A Japanese American friend who grew up eating natto suggests serving it mixed in steamed rice with soy sauce. This writer adds a heaping teaspoon of mustard and steamed vegetables. Stir well and repeat several times with quiet, firm conviction, “I will eat this,” then eat it quickly followed by something tasty like a small cluster of grapes or fresh apple slices.





Natto is available in Asian food stores, is inexpensive, servings are individually wrapped and must be refrigerated. Servings thankfully are small. Some PXE patients have decided to eat it once every two weeks, some once a month and others realize they can obtain K2 from other foods.

Fermented hard cheeses also provide K2. These are naturally aged cheeses which are more expensive than other cheeses. Fortunately, serving sizes should be small, perhaps only a tablespoon of grated cheese on a salad. So far we have identified the following hard cheeses available in the U.S.: Gorgonzola, Roquefort, Parmesan and semi-hard Munster. There are soft fermented cheeses also, but to date we are told by our doctors to use only those that are hard. We will continue to gather data on cheeses as this appears to be a good daily option for most of us. Remember – keep those servings small. Such cheeses also provide a high fat content.

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Another good daily option for Americans is sauerkraut, a fermented cabbage dish. In Germany and Eastern European countries, one can buy sauerkraut by weight from a barrel in almost any grocery store. In the U.S. those who have excellent deli stores may find fresh sauerkraut. Some groceries have it in jars in the refrigerated meat section – for example Clausen Sauerkraut. Nearby, one may find in plastic bags such brands as Boar's Head or Flanagan Krrrist Kraut. Other brands are available in jars or bags around the country. That in jars or bags must be refrigerated and seems more palatable than that available in cans. The canned variety is fermented, but it contains an extra portion of salt which makes it less fresh tasting. Donnie Carpenter of Fort Worth found his best choice to be kraut purchased from a local German restaurant. Once again, be reminded that a daily small serving is sufficient to meet known nutritional needs.

A suggestion for taking care of daily K2 nutrition is a small sauerkraut sandwich. Cut in half one slice of a hearty bread such as multigrain, whole wheat or rye, add a small amount of a favored condiment such as mayonnaise or mustard, a thin layer of grated hard-fermented cheese, a sprinkle of black pepper, a slice of fresh tomato and several tablespoons of sauerkraut. This makes a nice, quick, low calorie lunch and fulfills the need for Vitamin K2.



The list of K2 food sources provided by Dr. Struk includes a number of fat-rich red meats and dairy products. These should be eaten sparingly by PXE patients prone to cardiology problems.

We will continue to learn about Vitamin K food sources and will share them in future newsletters. We welcome information and suggestions for such sources and for ways to serve them.



## VITAMIN K

In 2000, the National Academy of Sciences established the following Adequate Intake (AI) levels for vitamin K:

Group	Age	Micrograms
Males and females	0-6 months	2
Males and females	7-12 months	2.5
Males and females	1-3 years	30
Males and females	4-8 years	55
Males and females	9-13 years	60
Males and females	14-18 years	75
Males	19 years and older	120
Females	19 years and older	90
Pregnant or lactating females	18 years and younger	75
Pregnant or lactating females	19 years and older	90

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### Basic Vitamin K food sources:

Food	Serving	Vitamin K (mcg)
Olive Oil	1 Tbsp	8.1
Soybean Oil	1 Tbsp	25.0
Canola Oil	1 Tbsp	16.6
Mayonnaise	1 Tbsp	3.7
Broccoli, cooked, chopped	1 cup	220.0
Kale, raw, chopped	1 cup	547.0
Spinach, raw	1 cup	145.0
Leaf lettuce (green), raw, shredded	1 cup	62.5
Swiss Chard, raw	1 cup	299.0
Watercress, raw, chopped	1 cup	85.0
Parsley, raw	¼ cup	246.0





## World's healthiest foods ranked as quality sources of: Vitamin K

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Food	Serving Size	Cals	Amount (mcg)
Parsley, fresh	2 tbs	2.7	123.00
Kale, boiled	1 cup	36.4	1062.10
Spinach, boiled	1 cup	41.4	888.50
Mustard greens, boiled	1 cup	21.0	419.30
Turnip greens, cooked	1 cup	28.8	529.34
Swiss chard, boiled	1 cup	35.0	572.80
Collard greens, boiled	1 cup	49.4	704.00
Romaine lettuce	2 cups	15.7	114.80
Basil, dried, ground	2 tsp	7.5	48.01
Thyme, dried, ground	2 tsp	7.9	48.01
Brussel sprouts, boiled	1 cup	60.8	218.80
Broccoli, steamed	1 cup	43.7	155.20
Cabbage, shredded, boiled	1 cup	33.0	73.35
Asparagus, boiled	1 cup	43.2	91.80
Oregano, dried, ground	2 tsp	9.2	18.65
Celery, raw	1 cup	19.2	35.26
Kelp (sea vegetable)	0.25 cup	8.6	13.20
Black pepper	2 tsp	10.9	6.88
Green beans, boiled	1 cup	43.8	20.00
Cloves, dried, ground	2 tsp	14.2	5.96
Cauliflower, boiled	1 cup	28.5	11.17
Tomato, ripe	1 cup	37.8	14.22
Green peas, boiled	1 cup	134.4	41.40
Carrots, raw	1 cup	52.5	16.10
Cayenne pepper, dried	2 tsp	11.2	2.89
Bell peppers, red, raw, slices	1 cup	24.8	4.51
Summer squash, cooked, slices	1 cup	36.0	6.30
Avocado, slices	1 cup	235.1	29.20
Miso	1 oz	70.8	8.53
Soybeans, cooked	1 cup	297.6	33.02
Cranberries	0.50 cup	23.3	2.42
Pumpkin seeds, raw	0.25 cup	186.7	17.73
Cow's milk, 2%	1 cup	121.2	9.76
Pear	1 each	97.9	7.47
Strawberries	1 cup	43.2	3.17
Papaya	1 each	118.6	7.90
Kidney beans, cooked	1 cup	224.8	14.87



# Salt Lake City Conference



Dr. Struk  
with sisters  
Cheri Moyer  
Jennifer Bly



Luncheon  
table talk

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Todd and Chris  
Stephens





# Salt Lake City Conference



Bill Guspie



Dennis Stapley

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Irene and Dick  
Speakman

Rosemary and  
Bob Atallian



# National Association for Pseudoxanthoma Elasticum

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Name of Loved One: \_\_\_\_\_

Address for Acknowledgement: \_\_\_\_\_

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PLEASE COMPLETE THE SECTION BELOW IF YOU HAVE PXE, THINK YOU HAVE PXE,  
OR ARE FILLING THIS OUT FOR SOMEONE ELSE

Name: \_\_\_\_\_ Phone: \_\_\_\_\_

Email: \_\_\_\_\_ Fax: \_\_\_\_\_

Address: \_\_\_\_\_

City: \_\_\_\_\_ State: \_\_\_\_\_ Zip: \_\_\_\_\_ Country: \_\_\_\_\_

Male  Female  Birthdate: \_\_\_\_\_ Age: \_\_\_\_\_

I am diagnosed with PXE  Yes  No      Newsletter:  Print  CD

Are you legally blind?  Yes  No       Email notification

Do others in your family have PXE?  Yes  No    If so, who? (Mother, Father, Sibling, etc. & Name) \_\_\_\_\_

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Please list any medical problem(s) you are experiencing: e.g., eye involvement, skin lesions, heart problems, gastric bleeding, etc., and comments/questions (use another page if required):

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Are you willing to be contacted by another who wishes to talk with someone else who has PXE?       Yes    No

## Have You Changed Your Address?

Please help by letting us know. Please be sure to print your new zip code number, including the extra four digits, if possible. When we use the full zip code, our costs of mailing in the United States are lower. Please help.

### *New Address*

Name: \_\_\_\_\_

Street: \_\_\_\_\_

City, State, Zip \_\_\_\_\_

### *Old Address*

Name, if different: \_\_\_\_\_

Street: \_\_\_\_\_

City, State, Zip \_\_\_\_\_

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