SOFT BONES, HARD ARTERIES: THE ROLES OF VITAMIN D, "THE OTHER K", AND ANTIBIOTICS.

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Three "parallel" lines of research intersect: (1) cardiovascular research into arterial and aortic-valve calcification, (2) vitamin K research, (3) vitamin D research. An informal survey found that specialists whose patients took a vitamin K-blocking anticoagulant (warfarin) were all unaware there were two kinds of vitamin K (K1 = phylliquinone, K2 = menaquinones) and unaware of implications for arterial and aortic valve calcification; all knew "green leafy vegetables" lowered INR but none knew of calcium-modulating K2 nor its bacterial origins. Vitamin K is recognized as a possible confound in vitamin D studies (Stojanovic et al. 2011), but rarely explored in research on Vitamin D's role in osteoporosis and cardiovascular calcification. Vitamin K researchers noticed the "calcification paradox" of soft bones and hard arteries early. Cardiovascular researchers tended to see this as due to "aging", but recently looked closely at the role of inflammatory signals in both (Hjortnaes et al. 2010). K2's blocking of inflammatory signals fits into that paradigm (Matsuda et al. 2010, Ohsaki et al. 2010, Yamaguchi & Weitzmann 2011) in ways congruent with D's complex immunological interactions (Hewison 2012). Kidd (2010) discusses synergy of D and K2 and possible mechanisms. Conversely, arterial calcification by high-dose vitamin D was accelerated when warfarin interfered with K2 (Price et al. 2000). Does the U-shaped function of D benefit/harm (Stojanovic et al. 2011) depend partly on vitamin K status of subjects? Does antibiotic use with humans and food animals exacerbate widespread K2 deficiency? Adequate coagulation can mask deficient calcification control by K2.

----> Plus (too late to include in Abstract)<---- K2 & bleeding disorders in newborns.

Three "parallel" lines of research intersect:
(1) cardiovascular research into arterial and aortic-valve calcification,
(2) vitamin D research,
(3) vitamin K research.

the cardiovascular line

I cannot pretend to an encyclopedic survey of all cardiovascular research, but my impression is:

● From the beginning there was controversy over whether trauma alone or infection alone could lead to calcific lesions or both were required. [for example, Gilbert & Lion 1889, Croq 1894, Bailey 1917]
This persisted for decades, and the presumed decades-long latency of sequelae of early infections was questioned.

● Very early, similarities between calcification in bone and in cardiovascular lesions were discounted, and a focus on lipids in vascular lesions was favored.
["...We have found that bone formation and pathological calcareous infiltration are wholly distinct processes. In the former there is no evidence of associated fatty change..." (Klotz, 1905)]

● After ignoring the "calcification paradox" (soft bones, hard arteries) or citing an asociation in the language of explanation (both "due to old age"), cardiovascular researchers began to look for possible common mechanisms -- almost too many to list in some reviews [e.g. Farhat & Cauley, 2008] -- but for some even the communality of arterial and valvular calcification continued to require investigation [Farhat & Cauley, 2008].

● Vitamin D and vitamin K began to be mentioned in omnibus reviews, but were not much explored in mainstream cardiovascular research. (Much focus on statins, etc.)

● Finally, a serious look at common mechanisms of deranged calcium metabolism and the "calcification paradox" focused on inflammatory mechanisms [Hjortnaes et al. 2010]

the vitamin D line

I cannot pretend to an encyclopedic survey of all vitamin D research, but my impression is:

● Early focus was primarily on relevance to bone.

● Relevance of vitamin D to vascular calcification was noted more than 1/2 century ago. [for example, Price & Sookochoff, 1969]

● Confrontation of the "calcfication paradox" came rather late. [Fujita et al., 1984; Kruger & Horrobin, 1997; Watson et al., 1997]

● Very late, vitamin K began to be recognized as a "potential confound" in vitamin D studies [Stojanovic et al. 2011]

● However, exploration of this "potential confound" continued to be rare.

● Does the U-shaped function of D benefit/harm (Stojanovic et al. 2011) depend partly on vitamin K status of subjects (usually unknown)?

● Arterial calcification by high-dose vitamin D was accelerated when warfarin interfered with K2 [Price et al. 2000]

● An important realm for exploration of communalities among calcium derangement in bone and vasculature (as seen in both cardiovascular and vitamin D research) was opened when research focused on vitamin D's immunological & inflammatory roles [see review by Hewison, 2012].

the vitamin K line

I cannot pretend to an encyclopedic survey of all vitamin K research, but I have read a lot of it.

● Understandably, in its earliest decades, vitamin K research focused on coagulation. However, there are suggestive titles beginning as early as 1947 suggestive of clinical observations relevant to calcification.

● Fundamental chemical studies in 1975 [Zytkovicz & Nelsestuen, 1975] led quickly to investigation of physiological relevance:
"...our findings may implicate vitamin K metabolism in normal bone development and suggest a role for the gamma-carboxyglutamate-rich protein in regulation of calcium salt deposition in mineralized tissues." [Hauschka, Lian, & Gallup, 1975]

● Even before this (4 years before), a role for vitamin K was seen in postmenopausal osteoporosis [Tomita, Fujita et al., 1971]. What is even more astonishing is that this 1971 study specified not just "vitamin K", but **vitamin K2** as the important variable.

● Studies of arterial & skeletal consequences of K deficiency (especially due to warfarin or antibiotic use) and K's relevance to the "calcification paradox" have followed [e.g. Adams & Pepping , 2005].

● Kidd (2010) discussed synergy of D and K2 and possible mechanisms. K2's blocking of inflammatory signals fits it into current paradigms of both "cardiovascular" and "vitamin D" research [Matsuda et al. 2010, Ohsaki et al. 2010, Yamaguchi & Weitzmann 2011]

Specialists with patients on warfarin:
(1) didn't know there are 2 kinds of vitamin K;
(2) didn't know the relevance of K2 deficiency to aortic valve calcification.

[all knew "green leafy vegetables" lowered INR but none knew of calcium-modulating K2 nor its bacterial origins]

It was an informal survey, but included every practitioner encountered for nearly a year, early 2011 - early 2012, in several disciplines, at more than one major medical center in NYC.

INCLUDED IN THE SURVEY:
3 cardiologists + several cardiology residents
1 neurologist + several residents (on a stroke unit)
1 cardiac surgeon + several residents
6 or more Ph.D. Nurse Practitioners
(several Nurse Practitioners attached to an Anti-Coagulation Clinic and others working with cardiologists evaluating patients for valve replacement and with cardiac surgeons).

Does antibiotic use with humans and food animals exacerbate widespread K2 deficiency? Adequate coagulation can mask deficient calcification control by K2.

● It is well known that antibiotics can interfere with vitamin K, in more than one way, and their effects can influence INR values and require adustment of warfarin doses.

● Besides effects of some classes of antibiotics on both K's (which could be by direct interference with vitamin K metabolism), they can also abolish production of K2 by gut bacteria.

● Cumulative effects on calcium distribution controlled by K2 might be seen only belatedly, because K1 may be adequate for normal coagulation.

● Dietary habits (some due to "health conscious" cholesterol phobia) put most US residents at risk for chronic K2 deficiency, and widespread personal use of antibiotics can exacerbate this.

● Unknown: the possible role of depletion of K2 in food animals due to widespread use of antibiotics in meat animals, dairy animals, and egg-producers (chickens).

LATE-BREAKING NEWS!
(too late to include in Abstract)
Someone needs to tell pediatricians about K2!

- One of the strangest counter-intuitive phenomena of neonatology is the perverse contradiction of the many benefits of breast-feeding by human mothers: breast-feeding has been seen for many decades as the major risk-factor for

HDN: "hemorrhagic disease of the newborn"

- Both prophylaxis and treatment traditionally speak only of "vitamin K", and it is clear that this means K1 (no mention of K2 in dozens -- hundreds? -- of publications).

- The explanations for vitamin K deficiency in neonates who are breast-fed focus on the presumed barriers for vitamin K transmission through the placenta and through mammary glands.

- However, studies which look at K2 (and sometimes compare K2 with K1) suggest that with normal K2 supplies (via diet and/or via gut bacteria), mothers can provide K2 via placenta and milk better than has been assumed. [Kamao et al. 2007, Kojima et al. 2004, Saga & Terao, 1989, Isshiki et al. 1988, Motohara et al. 1989, Tamura et al. 1984]

PEOPLE OFFERING ALTERNATIVE MODELS ARE UP AGAINST A PERSISTENT "BREAST-FEEDING" INDICTER WHO DOESN'T THINK HIGHLY OF K2 EITHER:

"...The breastfed infant has limited sources of vitamin K, as it is transmitted poorly across the placenta and is present in very low concentrations in human milk. The author of this paper reports a concentration of vitamin K in human milk (0.517 +/- 1.521 microg/dl) that is about twice the average of earlier reports (0.25 microg/dl). About half of the increased concentration (0.235 +/- 0.144 microg/dl) is accounted for by vitamin K2 (menaquinone) rather than vitamin K1 (phylloquinone); the latter generally thought to be more important in human nutrition..." [Greer, 2004: comment on Kojima et al. 2004]

It may be relevant that these women were Japanese, whose diet may have included more K2 than is common in US women.