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Vitamin K: The missing link to prostate health

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ABSTRACT

Though age-related prostate enlargement is very common in Western societies, and the causes of benign prostate hyperplasia, BPH, have been diligently sought after, there is no biological, mechanistic explanation dealing with the root causes and progression of this very common disorder among men. All treatments to date are based on symptomatic relief, not a fundamental understanding of the cause of the disease. However, recent advances have shown that even subclinical varicoceles, which are more common than generally realized, cause retrograde blood flow from the testes past the prostate gland causing over a 130-fold increase in free testosterone in the veins near the prostate. By treating the varicoceles via embolization of the internal spermatic vein and its communicating and connected vessels the prostate enlargement can be reversed with corresponding symptomatic relief. So, varicose veins in the pampiniform venous plexus, varicoceles, are the direct cause of BPH. But what causes varicoceles?

Recent research has uncovered the role of vitamin K in the calcification of varicose veins as well as a role in the proliferation of smooth muscle cells in the media layer of the vein wall. Vitamin K is intimately involved in the formation of varicose veins. The hypothesis is that poor prostate health is essentially a vitamin K insufficiency disorder. By providing vitamin K in the right form and quantity, along with other supporting nutrients and phytochemicals, it is likely that excellent prostate health can be extended much longer, and perhaps poor prostate health can be reversed. A protective role for vitamin K with respect to advanced prostate cancer was already found in the Heidelberg cohort of the EPIC study. This hypothesis can be further evaluated in studies examining the connection between vitamin K and varicoceles, and also by examining the connection between varicoceles and benign prostate hyperplasia. If this hypothesis is found to be true, management of prostate health will be radically altered. Rather than focusing on prostate health as a hormonal imbalance, prostate enlargement will be seen as a result of poor health of the veins in general and the internal spermatic veins in particular. Factors which promote the health of the veins will become a greater focus of research, including the role of vitamin K. Finally, the emerging understanding of the cause of BPH will empower men to take care of their bodies so they can enjoy much better health through their entire lifespan.

Introduction

Poor prostate health is pervasive in western society, especially with advancing age. The gradual enlargement of the prostate gland occurs in most men. The histologic prevalence of this swelling, known as benign prostatic hyperplasia, is approximately 10% for men in their 30s, 20% for men in their 40s, between 50% and 60% for men in their 60s, and is 80–90% for men in their 70s and 80s [1]. For a time this swelling appears not to result in symptoms, but for many men lower urinary tract symptoms become severe enough to seek medical care.

Even after decades of research, there is no clear understanding of the risk factors for BPH, and no clear understanding of the biological progression of the disorder. Obesity, diabetes, and some components of the metabolic syndrome have been associated with BPH [2]. Testosterone is obviously involved, as eunuchs do not have any occurrence of BPH [3]. However, serum testosterone concentrations decrease with age while occurrence of BPH increases. Nor do serum testosterone concentrations correlate with severity of the disorder [4]. The enzymatic transformation of testosterone by 5α-reductase into dihydroxytestosterone within the prostate is also a key step in the progression and a key target for pharmacological intervention. But the starting point of the hyperplasia has not been uncovered. Neither clinical nor epidemiological research has revealed the key to understanding BPH.

Recently, Dr. Gat and coworkers demonstrated a different treatment of BPH, based on a new understanding of the plight of the malfunctioning prostate gland [5,6]. Initially their work in interventional radiation treatment dealt with treating male infertility

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using a modified embolization protocol based on the original work of Comhaire and Kunnen [7]. One of the principal causes of male infertility was found to be varicoceles, or varicose veins in the pampiniform venous plexus. The molecular level causes of varicose veins are still debated. Varicose veins could result from failure of the one-way valves, or it could be the inflammation, proliferation of smooth muscle cells, and abnormalities in the extracellular matrix of the vein that then cause failure of the valves [8–10]. The varicose veins can be treated by microsurgery or by sealing off the internal spermatic vein and all accompanying and collateral or connecting veins. This therapy resolves the retrograde flow, normalizes the elevated blood pressure in the scrotum and often improves male fertility.

What Dr. Gat and coworkers discovered were two things. First, they saw that the retrograde flow from the testicular blood circulation emptied through the prostatic vein via connecting veins. This was important because when they measured testosterone concentrations in the blood reaching the prostate from the testes, both total testosterone and free testosterone were markedly higher than in the overall circulation. Free testosterone measured in the blood flowing to the prostate from 12 infertile men with varicocele averaged 3,632 pmol/l compared to 27.33 pmol/l in the serum, or about 130 times higher [5]. This markedly elevated concentration of testosterone would explain the hyperplasia seen in the prostate gland. Second, Dr. Gat and coworkers saw that all men with enlarged prostates had varicocele and when the varicocele was successfully treated the enlarged prostate was relieved of the physical pressure due to the elevated blood pressure caused by the height of the column of blood sitting in the internal spermatic vein and also was relieved of the hormonal pressure of the extremely high testosterone concentration. Blood was able to drain from the testicular circulation via normal venous pathways without causing retrograde flow past the prostate gland.

While the work of Dr. Gat and coworkers have lead to a treatment for BPH, they did not directly lead to a preventive strategy to lower the burden of the incidence of BPH. However, they demonstrated that the direct cause of BPH is varicocele.

The question then becomes finding the conditions that lead to varicocele. Though several factors are likely involved, some experiments and study reports have pointed to the role of vitamin K in arterial and venous health.

The hypothesis

The hypothesis is that poor prostate health is essentially a vitamin K insufficiency disorder. A vitamin K insufficiency leads to calcification of the media vein wall through the presence of inactivated MGP (matrix GLA protein), and proliferation of the smooth muscle cells in the media layer of the vein wall, setting the stage for varicosities to form. When the varicose vein forms in the pampiniform venous plexus, a varicocele, blood does not flow normally up the internal spermatic vein, but flows retrograde from the testicles directly to the prostate, causing a high local concentration of testosterone in the prostate, much higher than in the overall blood supply. This high concentration of free testosterone causes hyperplasia of the prostate. To prevent poor prostate health vitamin K must be provided in the amount and form that prevents the formation of varicoceles, in addition to other factors that are important for overall health and well-being.

Evaluation of the hypothesis

There are two lines of evidence that give some credibility to the hypothesis proposed here. First, in an examination of samples of varicose saphenous vein and normal saphenous vein tissue, Cario-Toumaniantz et al. [11] found that MGP (matrix GLA protein, a vitamin-K dependent protein) was over-expressed in varicose tissue compared to normal vein samples. More importantly, the form in the varicose tissue was also the uncarboxylated, inactive form, while in the normal veins the gamma carboxylated form of MGP dominated. The over-expression of MGP, along with increased mRNA expression of other extracellular matrix proteins such as collagen I, collagen III, TIMP I, dermatopontin, and tenascin C lead to proliferation of smooth muscle cells in the media of the veins. The increased amount of MGP led to a greater extent of mineralization in the media as well. In tissue cultures of smooth muscle cells for varicose and normal vein tissue, mineralization was increased by warfarin, a vitamin K inhibitor. In the varicose culture mineralization was dose-dependently inhibited by vitamin K, showing the direct connection between mineralization and lack of vitamin K. No investigation in this report was mentioned concerning Growth Arrest Specific Gene 6 (Gas-6) protein, though it is also a vitamin K dependent protein that affects smooth muscle cell apoptosis and movement. Regarding support for the present hypothesis, this work demonstrated a key role for vitamin K in varicose veins, both in the proliferation of smooth muscle cells and mineralization via its role in activating MGP.

A second line of evidence comes from the Heidelberg cohort of the EPIC (European Prospective Investigation into Cancer and Nutrition) study. Nimpstch et al. [12] found an inverse association between dietary intakes of vitamin K2, measured by FFQ (food frequency questionnaire), and risk of prostate cancer. There was a non-significant inverse relationship between menaquinone intake and total prostate cancer (multivariate risk for highest versus lowest quartile: 0.65; 95% CI: 0.39, 1.06), but there was a significant association between dietary vitamin K2 intake and advanced prostate cancer (0.37; 0.16, 0.88, p for trend = 0.03). There was no significant relationship with phylloquinone (vitamin K1) intake and prostate cancer (1.02; 0.70, 1.48).

A follow-up study using a nested case–control design from this same cohort identified an association between vitamin K status, measured by the ratio of undercarboxylated osteocalcin to intact total osteocalcin (ucOC/iOC), and prostate cancer risk. A significant 38% increase in risk of advanced stage prostate cancer for each 0.1 increment in the ucOC/iOC ratio, along with positive associations with high-grade prostate cancer and aggressive prostate cancer [13]. This study, using a biomarker for vitamin K status, eliminated questions in the initial study about inaccuracies in measuring vitamin K from dietary questionnaire and confirmed that there was a protective effect from higher intakes of vitamin K2.

While Nimpstch et al. pointed to the direct antiproliferation activity of the menaquinones to explain the benefits of vitamin K [12,13], the evidence is consistent with the hypothesis presented here, that vitamin K is protective for prostate health via prevention of varicocele. Indeed, the hypothesis does not nullify the more direct anti-cancer activity of vitamin K found in experiments, but shows that there may be more than one mechanism by which vitamin K is beneficial.

In an animal study vitamin K was shown to be effective in not only slowing but reversing arterial calcification in rats. By reversing the rat's arterial calcification induced by warfarin with high dietary vitamin K, Shurgers et al. [14] demonstrated that the degree of calcification is a dynamically controlled process rather than a static endpoint. It is then possible that calcification and its role in varicocele formation could be reversed, not only slowed or prevented.

This hypothesis gives an explanation for why the root cause of BPH has not been found by epidemiologists studying dietary intakes and health outcomes. Vitamin K2 appears to be the most effective form for arterial and venous health [12,15]. However, the foods that contain K2 are not in the "healthy" categories of

fruits and vegetables, nuts, seeds, and legumes. Vitamin K2's richest common sources are egg yolks, some cheeses, some cultured dairy products, and meat. Vitamin K2 can also be found in very high concentration in natto, a Japanese fermented soy product. Since a high consumption of sources of vitamin K2 are usually associated with negative health outcomes, it has been difficult to ascertain the benefits of vitamin K2 apart from the negatives health outcomes of high consumption of these foods. This confounding explains why it has been difficult to show vitamin K2 to be very important for prostate health.

There are two parts of this hypothesis that can be further verified. First, the connection between vitamin K and varicocele, and then the connection between varicocele and BPH. Using a case–control study design, healthy males without varicocele could be compared to age-matched males with varicocele, carefully measuring varicocele status as well as vitamin K status. Measurement of the percentage of undercarboxylated osteocalcin would be preferable and more accurate than food frequency questionnaires of vitamin K intake. By measuring vitamin K status and varicocele in any study design this part of the hypothesis could be tested. There are certainly other factors that contribute to the formation of varicoceles, so careful study design will be needed to take these factors into account.

Gat et al. [5] found that BPH did not occur without varicocele. This finding needs to be replicated and extended by other researchers. Note that visual inspection and palpation is not a sufficient method for detecting varicocele; Doppler sonography or contact thermography are much more sensitive in detecting even what are now considered subclinical varicoceles [16]. By using these sensitive detection methods the connection between varicoceles and prostate health could be easily verified or refuted.

Another way to verify the connection between BPH and varicocele is to screen men for varicocele who present to their physician with enlarged prostates. A consecutive series of men could be easily obtained and reported.

It is premature to propose an intervention study using a placebo-controlled, double-blind design to test whether vitamin K2 would prevent or treat BPH. Vitamin K2 is hypothesized to be a key nutrient in preventing varicose veins, but other factors are certainly also important. There are other nutrients and phytochemicals that strengthen and protect vein walls. Diosmin, derived from hesperidin extracted from citrus rinds, has been successfully used to lessen symptoms of chronic venous insufficiency [17,18]. Horse chestnut extracts have also had good effects [19], as well as proanthocyanidins from pine tree bark [20,21]. On the other hand, there are several factors that could negatively impact overall health and the health of veins in particular. Hypertension, obesity, diabetes, high fasting insulin, and low HDL cholesterol were all risk factors for BPH in a consecutive series of 158 men [2]. Supplementation with vitamin K2 alone is not likely to override these other risk factors, if present.

Consequences of the hypothesis and discussion

There are several consequences of this hypothesis. The foremost consequence, if this hypothesis is true, is that the strategy for managing prostate health will be radically altered. Rather than the primary interventions being medications for preventing the enzymatic conversion of testosterone into dihydrotestosterone, or surgeries of the prostate to remove impeding tissue, the focus will turn to treating varicoceles even when fertility is not a question. Rather than focusing on prostate health as a hormonal imbalance, prostate health will be seen as a result of poor health of the veins in general and the internal spermatic vein in particular. Factors which promote the health of the veins will become a greater focus of research. Vitamin K will be tested more extensively, and its role in vein health will be more thoroughly examined.

If this hypothesis is true, there will finally emerge a comprehensive, mechanistic, biochemical explanation of the causes of BPH, in which vitamin K plays a key part. By supporting healthy aging, including strengthening the walls and valves of the veins, the incidence of BPH can be dramatically reduced. Only by finally understanding the cause of poor prostate health can these advances be made. Prostate health will be seen as an extension of cardiovascular health, not a hormone imbalance. An evidence-based preventive program for BPH can be established. Using the knowledge of the importance of vein health, prevention can focus on vein health, with vitamin K's role being elevated to a critical position.

If this hypothesis is true, more research needs to be done on varicoceles because they relate to much more than just fertility. First, the incidence of varicoceles needs to be better quantified, especially among men over the age of 50. Surveys of the prevalence of varicocele among elderly populations have not been carefully done. In a retrospective study of 504 men with a mean age of 54.7 years it was found that about 75% of men in their eighth decade of life had varicocele [22], which is a far higher estimate than reported elsewhere. Canales et al. [23] found 42% incidence of varicocele in an elderly group of 354 men with a mean age of 60.7 years. However, only palpation was used to detect stage 1 varicoceles, so many subclinical varicoceles may have been missed.

If this hypothesis is true, people will likely increase their intake of vitamin K, both as vitamin K1 and vitamin K2. People will experience the side benefits of higher intakes of vitamin K, including fewer bone fractures [24,25], less arterial calcification [26,15], fewer cancer and cardiovascular deaths [27], and, for women, fewer cases of pelvic congestion syndrome [28]. Also, as more varicoceles are prevented more men will experience normal serum testosterone concentrations as they age, preventing early onset of a wide variety of diseases.

In conclusion, the hypothesis that poor prostate health is a vitamin K deficiency disorder is a plausible explanation that extends the work of Gat et al. [5]. Not only can varicoceles be treated, but understanding why they occur will empower men to take care of their bodies so they can enjoy much better health through their entire lifespan.

Conflict of interest

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References

[1] Roehrborn CG. Benign prostatic hyperplasia: an overview. Rev Urol 2005;7:S3–S14.
[2] Hammarsten J, Högstedt B, Holthuis N, Mellström D. Components of the metabolic syndrome-risk factors for the development of benign prostatic hyperplasia. Prostate Cancer Prostatic Dis 1998;1:157–62.
[3] Roehrborn CG. 5α-reductase inhibition in the treatment of LUTS and BPH: update and importance of dual inhibition of Types 1 and 2. Rev Urol 2004;6:S1–2.
[4] Zeng Q-S, Xu C-L, Liu Z-Y, Wang H-Q, Yang B, Xu W-D, et al. Relationship between serum sex hormones levels and degree of benign prostate hyperplasia in Chinese aging men. Asian J Androl 2012;14:773–7.
[5] Gat Y, Gornish M, Heiblum M, Joshua S. Reversal of benign prostate hyperplasia by selective occlusion of impaired venous drainage in the male reproductive system: novel mechanism, new treatment. Andrologia 2008;40:273–81.
[6] Gat Y, Gornish M. Reversal of benign prostate hyperplasia by super-selective intraprostatic androgen deprivation therapy. Eur Urol Rev 2009;4:10–4.
[7] Comhaire F, Kunnen M. Selective retrograde venography of the internal spermatic vein: a conclusive approach to the diagnosis of varicocele. Andrologia 1976;8:11–24.
[8] Elsharawy MA, Naim MM, Abdelmaguid EM, Al-Mulhim AA. Role of saphenous vein wall in the pathogenesis of primary varicose veins. Interact Cardiovasc Thorac Surg 2007;6:219–24.

[9] Oklu R, Habito R, Mayr M, Deipolyi AR, Albadawi H, Hesketh R, et al. Pathogenesis of varicose veins. J Vasc Interv Radiol 2012;23:33–9.
[10] Raffetto JD, Khalil RA. Mechanisms of varicose vein formation: valve dysfunction and wall dilation. Phlebol Venous Forum R Soc Med 2008;23:85–98.
[11] Cario-Toumaniantz C, Boularan C, Schurgers LJ, Heymann M-F, Le Cunff M, Léger J, et al. Identification of differentially expressed genes in human varicose veins: involvement of matrix Gla protein in extracellular matrix remodeling. J Vasc Res 2007;44:444–59.
[12] Nimptsch K, Rohrmann S, Linseisen J. Dietary intake of vitamin K and risk of prostate cancer in the Heidelberg cohort of the European prospective investigation into cancer and nutrition (EPIC-Heidelberg). Am J Clin Nutr 2008;87:985–92.
[13] Nimptsch K, Rohrmann S, Nieters A, Linseisen J. Serum undercarboxylated osteocalcin as biomarker of vitamin K intake and risk of prostate cancer: a nested case–control study in the Heidelberg cohort of the european prospective investigation into cancer and nutrition. Cancer Epidemiol Biomarkers Prev 2009;18:49–56.
[14] Schurgers LJ, Spronk HMH, Soute BAM, Schiffers PM, DeMey JGR, Vermeer C. Regression of warfarin-induced medial elastocalcinosis by high intake of vitamin K in rats. Blood 2007;109:2823–31.
[15] Geleijnse JM, Vermeer C, Grobbee DE, Schurgers LJ, Knapen MHJ, van der Meer IM, et al. Dietary intake of menaquinone is associated with a reduced risk of coronary heart disease: the Rotterdam Study. J Nutr 2004;134:3100–5.
[16] Gat Y, Bachar GN, Zukerman Z, Belenky A, Gornish M. Varicocele: a bilateral disease. Fertil Steril 2004;81:424–9.
[17] Gliński W, Chodynicka B, Roszkiewicz J, Bogdanowski T, Lecewicz-Toruń B, Kaszuba A, et al. The beneficial augmentative effect of micronised purified flavonoid fraction (MPFF) on the healing of leg ulcers: an open, multicentre, controlled, randomised study. Phlebology 1999;14:151–7.
[18] Jantet G. Chronic venous insufficiency: worldwide results of the RELIEF study. Reflux assessment and quality of life improvement with micronized flavonoids. Angiology 2002;53:245–56.
[19] Underland V, Saeterdal I, Nilsen ES. Cochrane summary of findings: horse chestnut seed extract for chronic venous insufficiency. Glob Adv Health Med 2012;1:122–3.
[20] Koch R. Comparative study of Venostasin and Pycnogenol in chronic venous insufficiency. Phytother Res 2002;16(Suppl. 1):S1–5.
[21] Petrassi C, Mastromarino A, Spartera C. PYCNOGENOL in chronic venous insufficiency. Phytomed Int J Phytother Phytopharm 2000;7:383–8.
[22] Levinger U, Gornish M, Gat Y, Bachar GN. Is varicocele prevalence increasing with age? Andrologia 2007;39:77–80.
[23] Canales BK, Zapzalka DM, Ercole CJ, Carey P, Haus E, Aeppli D, et al. Prevalence and effect of varicoceles in an elderly population. Urology 2005;66:627–31.
[24] Feskanich D, Weber P, Willett WC, Rockett H, Booth SL, Colditz GA. Vitamin K intake and hip fractures in women: a prospective study. Am J Clin Nutr 1999;69:74–9.
[25] Apalset EM, Gjesdal CG, Eide GE, Tell GS. Intake of vitamin K1 and K2 and risk of hip fractures: the Hordaland health study. Bone 2011;49:990–5.
[26] Beulens JWJ, Bots ML, Atsma F, Bartelink M-LEL, Prokop M, Geleijnse JM, et al. High dietary menaquinone intake is associated with reduced coronary calcification. Atherosclerosis 2009;203:489–93.
[27] Juanola-Falgarona M, Salas-Salvadó J, Martínez-González MÁ, Corella D, Estruch R, Ros E, et al. Dietary intake of Vitamin K is inversely associated with mortality risk. J Nutr 2014;144:743–50.
[28] Bittles MA, Hoffer EK. Gonadal vein embolization: treatment of varicocele and pelvic congestion syndrome. Semin Interv Radiol 2008;25:261–70.