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Association Between Vitamin D and Urinary Tract Infections

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An evidence-based scholarly paper submitted to the faculty of
Brigham Young University
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Master of Science

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ABSTRACT

Association Between Vitamin D and Urinary Tract Infections

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Urinary tract infections are a common infection that can have serious sequela. Many populations are susceptible to urinary tract infections. This article reviews emerging research that optimizing vitamin D levels can decrease risk of developing urinary tract infections. Recommendations are made for the health care provider based on the review of research.

Keywords: urinary tract infections, vitamin D, cathelicidin, hospital acquired infections, renal, kidney

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Introduction

More than ever since the advent of antibiotics, infections today pose a serious threat to the welfare of health care consumers. Hospital-associated urinary tract infections (UTIs) and catheter associated UTIs (CAUTIs) are one of the most common of the over 700,000 hospital acquired infections (HAIs) annually, leading to increased length of stay and even increased mortality (Magill et al., 2014). Not only is the human cost associated with UTIs and HAIs unacceptable, but the financial burden on today's health care is crippling to an already distressed system. In 1995, 11.3 million women were treated with antibiotics in the U.S. for UTIs, at an estimated cost of \$1.6 billion. At a rate of 5% annual inflation, the approximate 20-year cost for treatment of UTIs in women in the U.S. would be \$25.5 billion (Foxam, Barlow, D'arcy, Gillespie & Sobel, 2000).

The effects of UTIs are far reaching. Both males and females are susceptible to UTIs across the entire lifespan. Populations particularly at risk include infants, females, pregnant females, renal transplant populations, immune compromised individuals, and the elderly. Urinary tract infections can have significant lasting health effects, including progressive renal damage and failure, hypertension, pyelonephritis, endocarditis, septic arthritis, and meningitis. Effects exclusive to males can include chronic prostatitis, epididymitis, and orchitis (Center for Disease Control (CDC), 2016; Tekin et al., 2015). Urinary tract infections can be particularly risky in pregnancy, resulting in pre-term birth, intrauterine growth restriction, and pre-eclampsia (Ramos et al., 2014). Urinary tract infections are especially problematic in post-renal transplant patients and can lead to increased graft failure and higher mortality rates (Kwon et al., 2015).

Given the high rate of UTIs, soaring health care costs, possible harmful side effects, and even associated death, there is a need for Nurse Practitioners to implement strategies for UTI

prevention and improved treatment options. Recent research has indicated an association between increased UTI rates and vitamin D deficiency and insufficiency (Hacihamdioglu, et al., 2016; Jorde, Sollid, Svartberg, Joakimsen, Grimnes, & Hutchinson, 2016; Kwon, et al., 2015). The purposes of this clinical paper are to discuss: (a) vitamin D, (b) vitamin D deficiency and insufficiency, (c) factors influencing the development of a UTI and its relationship to vitamin D, and (d) to make clinical recommendations based on the findings.

Method

Electronic database searches were conducted to identify relevant studies. Databases included Medline, CINAHL, Pubmed, and the Cochrane Library. The search terms included were vitamin D, 25-hydroxyvitamin D3, 25(OH) D3, urinary tract infection, UTI, hospital-acquired infection, hospital-associated infection, catheter associated urinary tract infection, renal, kidney, infection, cathelicin, and cost. Inclusion criteria were peer reviewed studies in English, ranging from 2005–2017. A total of eight articles met the criteria for review, and these articles included one randomized controlled trial, five correlational studies, and two experimental design studies.

Background

Vitamin D

Vitamin D is an essential and unique steroid hormone. The major role of vitamin D is to maintain normal blood levels of calcium and phosphorus. Vitamin D also assists the body in absorbing calcium, which maintains strong bones. Ongoing research suggests the importance vitamin D might also play in protecting against osteoporosis, high blood pressure, cancer, and other diseases. Recent findings have linked vitamin D levels to immune system function.

Humans synthesize vitamin D in the skin when exposed to sunlight, which accounts for 90% of the vitamin D found within the body. The other 10% of vitamin D comes from dietary sources. However, naturally occurring food sources of vitamin D are rare; therefore, the majority of dietary vitamin D comes from fortified cereals, fortified dairy, and supplementation. Vitamin D from the skin or diet is metabolized in the liver to 25-hydroxyvitamin D (25[OH]D), then converted in the kidneys to 1, 25-dihydroxyvitamin D (D₃), which is the active, usable form of the vitamin (Crew et al., 2009).

Vitamin D Deficiency and Insufficiency

The U.S. Endocrine Society guidelines define vitamin D deficiency as serum vitamin D below 20 ng/ml (50 nmol/liter) and insufficiency as serum vitamin D of 21-29 ng/ml (52.5-72.5 nmol/liter) (Holick et al., 2011). According to these guidelines, the majority of the U.S. population is vitamin D insufficient or deficient.

Several environment factors and health related conditions can result from insufficient or deficient vitamin D levels. Inadequate exposure to natural sunlight is a major contributor to reduced levels because this is the major source of vitamin D for all ages. Furthermore, during the winter season due to decreased ultraviolet light from the sun there is reduced vitamin D synthesis. The Sun Belt, an area within 33 degrees latitude north and south of the equator, provides an adequate amount of sunlight during the entire year for those receiving sufficient exposure. Yet the further north or south from the Sun Belt one goes there is less sunlight, which reduces vitamin D levels. The majority of North America lies outside of the Sun Belt, and winter sun ultraviolet light exposure is very low, or essentially zero, which results in little to no vitamin D synthesis during these months (Holick et al., 2011). Adding to decreased levels is the use of sunscreen with an SPF of 30, which reduces vitamin D synthesis in the skin by greater than 95%.

Additionally, people with naturally darker pigmented skin need 3–5 times longer sunlight exposure to produce vitamin D than those with lighter skin tones (Holick et al., 2011).

Obesity is another contributing factor to inadequate vitamin D levels. Although the mechanism is not fully understood, there is an inverse association between serum vitamin D and a body mass index (BMI) of greater than 30/kg/m² (Holick et al., 2011). Factors that might contribute to this relationship include the possibilities that many obese people tend to cover their skin more with clothing, might lead sedentary lives, and perhaps do not go outside as much. In addition, vitamin D stored in fat remains there and is not in circulation for use (Hosseini-nezhad & Holick, 2013).

Elderly are also at risk for reduced vitamin D levels due to their decreased capacity to synthesize vitamin D in their skin. Their lifestyles also contribute to lower UV exposure in that they are more likely to be indoors, cover the skin with clothing, use sunscreen, and avoid direct sun exposure (Hosseini-nezhad & Holick, 2013).

Other groups might also be at risk for vitamin D deficiency. For example, post-bariatric surgery patients might be unable to absorb adequate levels of vitamin D. In addition, patients with kidney syndromes can lose vitamin D that is bound to protein in the urine (Holick et al., 2011). Finally, many medications can contribute to vitamin D deficiency, including glucocorticoids, antifungals, anticonvulsants, and medications to treat HIV/AIDS (Hosseini-nezhad & Holick, 2013).

Factors Influencing the Development of a UTI and its Relationship to Vitamin D

Evidence suggests that vitamin D might play a role in mitigating or eliminating the influence of bacteria in the urinary tract system. Knowledge of the anatomy of the urinary tract helps to understand how the tract can be compromised and result in an infection. The urinary

meatus is not sterile, but the rest of the urinary tract, including the urethra, bladder, ureters, and kidneys, does maintain sterility. Anatomy in females can make them prone to infections as the urethra is located close to the rectum leaving the meatus potentially exposed to numerous pathogenic organisms (Zasloff, 2007). Individuals requiring urinary catheterization are also at increased risk because catheters can introduce bacteria into the urinary tract and bladder. Several protective factors can help stop the development of a UTI and include the innate immune system and antimicrobial peptides (AMPS). Evidence suggests that vitamin D might play a role in supporting and enhancing these systems.

Innate Immune System

Although urine can very easily support the growth of bacteria, UTIs are often kept in check due to the innate immune system. The innate immune system is the first-line rapid response barrier to prevent microbial invasion. It is comprised of cells, proteins, and receptors that immediately recognize and neutralize foreign microbes. Most bacteria reproduction time is between 20 to 30 minutes. At this rapid rate, infections could easily overwhelm the body before the adaptive immune system is activated. This is why the quick response of the innate immune system is of vital importance in stopping UTI development (Johnston, 2016).

Components of the innate immune system include physical barriers, enzymes in epithelial and phagocytic cells, inflammation-related serum proteins, antimicrobial peptides (AMPS), cell receptors that sense microorganisms and signal a defensive response, cells that release cytokines and other inflammatory mediators, and phagocytes (Johnston, 2016). Optimization of the innate immunity is a key component in the defense against UTIs. Researchers have indicated that vitamin D can enhance antimicrobial peptides and promote phagocytosis, thus improving the protection provided from the body's innate immune system.

Antimicrobial Peptides

Antimicrobial peptides (AMPS) are proteins synthesized by immune and epithelial cells. These proteins bind to foreign microbes and neutralize them, offering instant protection (Luthje & Brauner, 2016). One such antimicrobial peptide in the urinary tract is cathelicidin (LL-37). Cathelicidin is constantly synthesized by urinary epithelium in uninfected tissue and released immediately without being stored. Once exposed to a foreign microbe, such as *E. coli*, cathelicidin levels rise within minutes, preventing colonization and infection (Zasloff, 2007). It is thought vitamin D might influence the induction of cathelicidin in the urinary bladder.

Research evidence supports the influence of vitamin D on the synthesis induction of cathelicidin in the urinary bladder. Post-menopausal women treated for 12 weeks with 2000 units of oral vitamin D3 serum 25-hydroxyvitamin D levels were found to have increased vitamin D levels at 6 and 12 weeks. Baseline levels were 27.4 ng/ml, at 6 weeks 41.8 ng/ml, and at 12 weeks 46.8 ng/ml. Bladder biopsies were taken before supplementation and after supplementation. The pre- and post-supplementation bladder biopsies were compared when exposed to *E. coli* and found that the post-vitamin-D supplementation bladder biopsy responded with a higher expression of cathelicidin ($p < 0.05$). Researchers concluded that cathelicidin production from urinary epithelial cells can be induced by increasing vitamin D levels (Hertting et al., 2010).

Results

Research studies show that there is evidence to support the positive effects of vitamin D on UTIs in the pediatric population, women, renal transplant patients, and prediabetic patients. Each of these will be discussed.

UTIs in Pediatric Population

Yang et al. (2016) compared 238 infants, 132 experiencing a first UTI and 106 controls, ranging in age from 1 month to 12 months. Serum vitamin D levels were significantly lower in the cases with UTI (29.09 +/- 9.56 ng/ml) versus the control group (38.59 +/- 12.41 ng/ml). The study concluded that serum 25 hydroxyvitamin D < 20 ng/ml significantly increased incidence of UTI in infants ($p = 0.012$). Additionally, the study concluded that infant vitamin D supplementation was associated with a decreased risk of developing a UTI ($p = 0.001$).

In Hacichamdioglu et al. 2016 study, serum vitamin D levels and urine cathelicidin levels were measured in 36 pediatric patients with a UTI (mean age 6.8 +/- 3.6 years) and compared with 38 control participants (mean age 6.3 +/- 2.8 years). The researchers found that patients with a UTI and sufficient levels of vitamin D had significantly higher urine cathelicidin levels than the controls with sufficient vitamin D levels ($p = 0.001$). The researchers concluded that children with vitamin D insufficiency are unable to adequately increase urine cathelicidin when exposed to urinary pathogens, which increases risk of UTI (Hacichamdioglu et al., 2016).

In a study done by Tekin et al. (2015) researchers compared 82 children with a first diagnosis of a UTI to 64 healthy control children. The comparison group did not have a UTI or any other risk factors. Researchers found the mean serum levels of vitamin D3 among the children with a UTI significantly lower than the control group (11.7 ng/ml +/- 3.3 vs. 27.6 ng/ml +/- 4.7). These researchers concluded that vitamin D3 levels of < 20 ng/ml was significantly associated with increased risk of UTI ($p < 0.001$) (Tekin et al., 2015).

Aslan et al.(2011) compared 92 children with a UTI to a control group of 105 healthy children without a prior history of a UTI. Researchers looked at small genetic alterations (polymorphisms) in vitamin D receptors (VDR) and susceptibility to UTIs. The VDR regions bind to vitamin D and encode for expression of cathelicidin. They found that the UTI group had

a significant increase of FokI (VDR) gene polymorphism. The risk of UTI was 3.94 times greater in groups with this FokI gene polymorphism. The findings resulted in an association between FokI VDR gene polymorphisms and UTI ($p < 0.01$) (2011).

UTIs in Women

Nseir, Taha, Nermarny, and Mograbi (2013) assessed whether there was an association between vitamin D levels and a risk of recurrent UTIs in premenopausal women. In this study, 93 premenopausal women aged 20–52 years with recurrent UTIs were compared to a control group of age matched women without history of UTIs. The groups had no clinical difference in terms of age, history of diabetes mellitus, maternal history of recurrent UTI, use of oral contraceptive, probiotic use, sexual intercourse frequency, or indoor/outdoor activities. A multivariate analysis showed that the following associations for recurrent UTIs: maternal history of recurrent UTIs ($p = 0.05$); no use of probiotics ($p = 0.04$); and most significantly, serum vitamin D < 15 ng/ml ($p = 0.001$). Vitamin D levels were significantly lower in the recurrent UTI group (9.8 ng/ml \pm 4 vs. 23 ng/ml \pm 6).

UTIs in Renal Transplant Patients

Kwon et al. evaluated vitamin D deficiency and UTI rates in post-renal transplant patients. The study followed 410 renal transplant patients over 7 years, looking at vitamin D levels and UTI rates. The researchers found that post-renal transplant UTI rates were significantly higher in patients with vitamin D deficiency ($p = 0.001$). Vitamin D deficiency was an independent predictor of UTIs in these patients (2015).

UTIs in Pre-Diabetic Patients

In a randomized controlled study, 511 subjects with pre-diabetes were randomized to receive placebo ($n = 255$) or vitamin D 20,000 IU ($n = 256$) weekly. The subjects were followed

for 5 years. Every 6 months they returned a questionnaire on respiratory infections and UTIs. One hundred eleven of the placebo group, and 116 of the vitamin D supplementation group completed the 5-year study. There were no differences in the two groups with respiratory infections, but there were significant differences with UTIs. Within the 5 years, 34 subjects in the placebo group and 18 subjects in the vitamin D group developed a UTI ($p < 0.02$). The study concluded that vitamin D supplementation can lower risk of UTIs (Jorde et al., 2016).

Discussion

This clinical paper has focused on the link between vitamin D levels and UTI rates in specific populations: pediatric, premenopausal women, post-renal transplant patients, and pre-diabetic adults. The reviews also focused on vitamin D levels and cathelicidin production in bladder cells. This research has established the link between adequate vitamin D levels and increased cathelicidin productions. This relationship boosts the innate immune system, which offers protection from UTI development. Correlational studies support these findings. Weaknesses of current correlational studies include small, area-focused sample sizes.

The optimal levels of vitamin D have not been studied and determined in relationship to UTI protection. For example, we know serum levels less than 30 ng/ml are not good for bone health, but perhaps levels of 50 ng/ml or 60 ng/ml might be needed to provide optimization of the innate immune system. Further studies are needed to support what levels are optimal for urinary tract health.

Jorde et al. (2016) in a randomized controlled study of pre-diabetic subjects found relationship between vitamin D supplementation and lower UTI rates. But additional randomized controlled trial studies of vitamin D supplementation and UTI rates should be done on different populations to solidify the relationship.

Finally, with the increased rate and mortality associated with hospital acquired infections (HAIs), research is needed to evaluate vitamin D supplementation within the hospital setting to help prevent HAIs.

Implications for Practice

Nurse practitioners can play an integral role monitoring, educating, and ensuring adequate vitamin D levels in their patients. The decision to screen a patient's vitamin D level is made with careful consideration of potential vitamin D deficiency, risk factors, certain disease processes, and cost of the screening. Serum 25-hydroxyvitamin D (25[OH]D) is the lab level used for screening. When a blood test is recommended to monitor serum vitamin D levels, a follow up serum vitamin D level is recommended at 3 months after starting supplementation, and then yearly after that (Aungst & Rainer, 2014).

A vitamin D level of < 20 ng/ml has historically been used in practice to indicate prescription treatment of inadequate vitamin D. In the U.S., the typical prescription treatment for adults requiring vitamin D supplementation is high dose oral ergocalciferol (D2) 50,000 IU once a week for 6–8 weeks. After that time, most patients can transfer to an over the counter oral daily dose of 1,000 IU vitamin D3 daily (Collins, 2013).

The U.S. Endocrine Society (2011) made the following recommendation for daily vitamin D supplementation. (Insert Table 1)

In certain populations with malabsorption processes or inability to swallow, there is intramuscular injectable cholecalciferol. Additionally, narrowband UV B radiation light therapy can be used for patients to increase vitamin D levels (Collins, 2013).

Vitamin D supplementation is fairly inexpensive, very low risk for patients, and easily accessible. Its use would be beneficial to consider as preventative treatment in UTI susceptible

populations. It is extremely rare and difficult to develop vitamin D toxicity, which is typically due to ingesting exceedingly high doses of vitamin D >50,000-100,000 IU for months to years, making the likelihood of vitamin D overdose very low (Holick, 2015). Further consideration should be made regarding whether in-patient populations should be screened and with treated with vitamin D to decrease HAIs.

Conclusion

UTIs are one of the most common infections. Many are susceptible to UTIs and there are serious side effects. This review of current literature concludes that inadequate vitamin D levels can contribute to UTI rates and vitamin D supplementation can be a low risk option to help prevent UTIs. The nurse practitioner can play an integral role in identifying at-risk individuals, screening, educating, and treating. Although further research is needed, vitamin D can be part of the answer to individuals susceptible to UTIs and in-patient populations who are at risk of HAIs.

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tract. *Journal of American Society of Nephrology*. 18, 2810–2816.

Table 1*Age-Based Vitamin D Supplementation Recommendation*

Age	Vitamin D IU (IU = 25ng)
0–1	400 IU/day
1–18	600–1000 IU/day
19–70+	600–2000 IU/day
Pregnant/lactating females	600–2000 IU/day

* To maintain serum level vitamin D above 30 ng/ml

* Obese individuals and those taking anticonvulsant, antifungal, glucocorticoids, and HIV/AIDs medications might need 2-3 times vitamin D supplementation to satisfy their body's vitamin D requirement. (Holick et al., 2011)