International Journal of Infectious Diseases 17 (2013) e1121–e1124

Contents lists available at SciVerse ScienceDirect

International Journal of Infectious Diseases

journal homepage: www.elsevier.com/locate/ijid

The association between serum levels of vitamin D and recurrent urinary tract infections in premenopausal women

William Nseir [a,b,c,*], Muhamad Taha [b], Hytam Nemarny [a], Julnar Mograbi [a]

[a] Department of Internal Medicine, EMMS Nazareth, The Nazareth Hospital, Nazareth, Israel
[b] Infectious Diseases Unit, EMMS Nazareth, The Nazareth Hospital, Nazareth, Israel
[c] Faculty of Medicine in the Galilee, Bar-Ilan University, Safed, Israel

ARTICLE INFO

Article history:
Received 27 March 2013
Received in revised form 7 June 2013
Accepted 10 June 2013

Corresponding Editor: Eskild Petersen, Aarhus, Denmark

Keywords:
Recurrent urinary tract infections
Vitamin D
Premenopausal women

SUMMARY

Objectives: To examine whether there is any association between serum levels of 25-hydroxy vitamin D (25(OH) vitamin D) and the recurrence of urinary tract infections (UTIs) among premenopausal women.
Methods: During a period of 3 years, 93 premenopausal women with a medical history of recurrent UTIs were enrolled from the Infectious Diseases Unit. Cases with recurrent UTIs were compared to 93 age-matched (±5 years) women with no history of recurrent UTI (control group), in terms of serum 25(OH) vitamin D and different risk factors for recurrent UTI. Recurrent UTI was defined as three or more episodes of UTI over a 12-month period.
Results: The mean age of women with recurrent UTIs was 43.8 ± 9 years and of controls was 39 ± 10 years ($p = 0.839$). The mean serum levels of 25(OH) vitamin D among women with recurrent UTIs were significantly lower than those of controls (9.8 ng/ml ± 4 vs. 23 ng/ml ± 6; $p < 0.001$). Multivariate analysis showed that a serum 25(OH) vitamin D level of < 15 ng/ml (odds ratio 4.00, 95% confidence interval 3.40–4.62; $p = 0.001$) was associated with recurrent UTIs in premenopausal women.
Conclusions: In this retrospective study, we found that recurrent UTIs in premenopausal women are associated with vitamin D deficiency.
© 2013 International Society for Infectious Diseases. Published by Elsevier Ltd. All rights reserved.

1. Introduction

Urinary tract infection (UTI) is one of the most commonly acquired bacterial infections in ambulatory and hospitalized populations. Approximately 11% of all women aged ≥18 years in the USA have a UTI each year. The incidence of UTI is highest among women aged 18–24 years, approaching one of five infections per year.[1] The incidence of UTIs in Israel is not so well known, as there is a lack of epidemiological studies on this topic. Although, the risk of bladder UTI (cystitis) progression to pyelonephritis is negligible among otherwise healthy women, cystitis has a propensity to recur. Among healthy women aged 18–39 years, the 6-month risk of recurrence following a first UTI is 24%.[2] Approximately 5% of women with an initial UTI have multiple episodes within a year. Major risk factors for UTI among women aged 18–39 years are engaging in sexual intercourse and having a history of UTI.

Treating UTIs with antibiotics selects for antibiotic resistance among uropathogens and other bacteria found in and on the human body. In the USA, and worldwide, uropathogens are increasingly resistant to antibiotics.[3–7] Women with recurrent UTIs are prescribed repeated courses of antibiotics both as treatment and as a preventive strategy. Because antibiotic therapy is a major driver of resistance and adversely affects the normal microbiota, preventive strategies that reduce the need for antibiotic therapy are particularly important.

Vitamin D deficiency has been associated with several adverse health consequences, including autoimmune diseases and infections.[8–10] The results of epidemiological studies have demonstrated the existence of a link between vitamin D deficiency and the increased occurrence of pulmonary tuberculosis and respiratory infections.[11,12] Recently we showed an association between low serum levels of 25-hydroxy vitamin D (25(OH) vitamin D) and the risk of recurrent bacterial infections.[13–15]

Against this background, we conducted this retrospective study in order to examine whether there is any association between the serum levels of 25(OH) vitamin D and the risk of recurrent UTIs in premenopausal women.

* Corresponding author. Tel.: +972 747559050; fax: +972 747559051.
E-mail address: w.nseir@yahoo.com (W. Nseir).

1201-9712/$36.00 – see front matter © 2013 International Society for Infectious Diseases. Published by Elsevier Ltd. All rights reserved.
http://dx.doi.org/10.1016/j.ijid.2013.06.007

2. Materials and methods

2.1. Subjects

We included all premenopausal women with recurrent UTIs who were followed-up between 2009 and 2011 at the Infectious Diseases Unit of EMMS, a 170-bed primary care hospital in Nazareth, Israel. Premenopausal women aged 20–52 years who had not received antibiotic prophylaxis for recurrent UTIs, including post-coital, were included. The exclusion criteria were: (1) pregnancy, and (2) chronic renal failure (creatinine clearance test <30 ml/min), a chronic liver disease, a malignancy with life expectancy less than 1 year, HIV infection, connective tissue diseases, permanent urinary catheter, urinary tract stent, nephrostomy tube, urinary incontinence, neurogenic bladder, asymptomatic bacteriuria, kidney malformations, kidney stones, gynecological problems, organ transplant, chronic use of corticosteroid therapy, vitamin D supplementation, and substance abuse.

Control cases were premenopausal women with no medical history of UTI, randomly collected from the Medicine Clinic and Employee Health Clinic, EMMS, who were age-matched ±5 years; the same exclusion criteria were used. The matching was performed on a group, rather than individual level. For each case of recurrent UTI we recruited one control case. The study was approved by the review board of EMMS.

2.2. Study design

This was a retrospective study aimed at examining the association between serum 25(OH) vitamin D levels and recurrent UTIs in premenopausal women. In order to assess this, we compared the two groups of premenopausal women – with and without recurrent UTIs – in term of: diabetes mellitus (DM), maternal history of recurrent UTIs, oral contraceptive use, probiotics, cranberry juice consumption, sexual intercourse, and serum levels of 25(OH) vitamin D.

2.3. Clinical and laboratory data

Information concerning medical conditions and drug therapy, and the results of laboratory analyses, were extracted from the medical charts of each subject in the two groups. (In general, every subject who visits the Infectious Diseases Unit/Medicine Clinic/the Employee Health Clinic, completes a standard questionnaire at every visit concerning their medical condition, drug therapy, family history of different diseases, systemic bacterial infections, and results of laboratory analyses, including urinalysis and urine culture.) The results of chemistry analysis, including fasting blood glucose, hemoglobin A1c (HbA1c), serum creatinine, serum calcium, and a complete blood count, were collected from the medical charts. Serum 25(OH) vitamin D levels were measured in winter and summer seasons (at least twice a year) for all patients visiting our units. Serum 25(OH) vitamin D levels were measured using a commercial kit (IMM, Bensheim, Germany), by enzyme immunoassay (EIA). The normal range of serum 25(OH) vitamin D levels is 30–50 ng/ml.

2.4. Definitions

UTI was defined by clinical signs of dysuria and the urgency and frequency of urination (cystitis), and the presence of fever, chills, and/or loin pain (pyelonephritis). Bacterial UTIs included cystitis, urethritis, and acute pyelonephritis.[16] Recurrent UTI was defined as a symptomatic UTI following the resolution of a previous UTI and of three or more symptomatic episodes over a 12-month period.[17] All case patients had to have recurrent UTIs including one or more culture-confirmed UTI; the UTI could be a case of re-infection or relapse. Re-infection refers to a new infection, i.e. the urine shows no growth after the previous infection, but the same organism grows again at 2 weeks after treatment, or a different strain is grown at any time. A relapse refers to a UTI caused by the bacterial strain from a focus inside the urinary tract within 2 weeks of treatment. Normal levels of serum creatinine are 0.67–1.17 mg/dl and of serum calcium are 8.1–10.4 mg/dl. We defined vitamin D insufficiency as levels of 25(OH) vitamin D 20–30 ng/ml, and vitamin D deficiency as levels of 25(OH) vitamin D <20 ng/ml.

2.5. Statistical analysis

WinSTAT (Kalamia, Cambridge, MA, USA) was used for data handling and analysis. Mean values, standard deviations (SDs), and p-values were calculated. The Chi-square test was performed for categorical variables, and the Student's t-test was used for continuous variables. Spearman rank correlation and univariate regression analysis were used to determine the strengths of the relationships between the different risk factors and recurrent UTIs. A risk factor associated with a p-value of <0.05 in the univariate analysis was used for further analysis. A multivariate analysis was performed to determine the association between the risk factors and recurrent UTIs. Statistical significance was set at 5%.

3. Results

Of 265 women followed-up in the Infectious Diseases Unit for UTIs during the study period, 93 premenopausal women with recurrent UTIs met the inclusion criteria. One hundred and seventy-two subjects were excluded because of: postmenopausal (n = 41), no recurrent UTI (n = 60), pregnancy (n = 7), chronic renal failure (n = 19), liver cirrhosis (n = 7), malignancy with life expectancy <1 year (n = 16), permanent urinary catheter (n = 7), kidney stones (n = 5), chronic steroid use (n = 3), and vitamin D use (n = 7). Table 1 shows the clinical and laboratory parameters of the cases with recurrent UTIs and the controls. No significant difference was found between the cases and controls in terms of age, DM, maternal history of recurrent UTIs, oral contraceptive use, probiotics, sexual intercourse, and indoor/outdoor activities. No

Table 1
A comparison of certain clinical and laboratory parameters between cases with recurrent UTIs and controls

	Cases with recurrent UTI (n=93)	Controls (n=93)	p-Value
Age, years, mean ± SD	43.8 ± 9	39 ± 10	NS
Diabetes mellitus, n (%)	26 (28%)	20 (21.5%)	NS
Maternal history of recurrent UTI, n (%)	13 (14%)	6 (6.5%)	NS
Use of oral contraceptives, n (%)	2 (2.2%)	4 (4.3%)	NS
Use of probiotics, n (%)	2 (2.2%)	6 (6.5%)	NS
Sexual intercourse ≥1 per week (%), n (%)	45 (48%)	54 (58%)	NS
Serum 25(OH) vitamin D, ng/ml, mean ± SD	9.8 ± 4	23 ± 6	<0.001
Indoor, n (%)	82 (88%)	78 (84%)	NS

UTI, urinary tract infection; SD, standard deviation; NS, not significant.

subjects in the two study groups were using cranberry juice as prophylaxis. However, compared to the control group, serum 25(OH) vitamin D levels were significantly lower in the cases (9.8 ng/ml ± 4 vs. 23 ng/ml ± 6, respectively; $p < 0.001$). The lowest 25(OH) vitamin D level was 4 ng/ml, which was found in one subject who suffered from recurrent UTIs (at least 6 episodes/year); the highest level was 46 ng/ml, which was found in one subject in the control group. All study participants were of the same race.

Multivariate analysis showed that a maternal history of recurrent UTIs (odds ratio (OR) 1.60, 95% confidence interval (CI) 1.40–2.60; $p = 0.05$), no use of probiotics (OR 1.94, 95% CI 1.61–2.82; $p = 0.04$), and serum 25(OH) vitamin D <15 ng/ml (OR 4.00, 95% CI 3.40–4.62; $p = 0.001$), were associated with recurrent UTIs in premenopausal women. The multivariate analysis results are shown in Table 2.

4. Discussion

In this retrospective study, we found that vitamin D deficiency in premenopausal women was independently associated with recurrent UTIs.

The mechanism(s) that link vitamin D deficiency with recurrent UTI are unknown. There are many host defense factors in the urinary tract, such as the Tamm–Horsfall protein, lipocalin, and lactoferrin, which offer some protection from infection.[18] Infections of the urinary tract induce epithelial cells to produce cathelicidin LL-37, protecting against bacterial infection.[19] Vitamin D is a potent stimulator of antimicrobial peptides including cathelicidin LL-37 in innate immunity.[20] Recently, Hertting et al. observed a significant increase in cathelicidin in response to vitamin D in biopsy samples of urinary bladder infected by uropathogenic *Escherichia coli*.[21] In humans, the production of cathelicidin and some defensins depends upon vitamin D levels, particularly during the infection process.[22] Previous studies have shown the importance of vitamin D for innate immunity in defending against bacterial infections, mainly by increasing the neutrophilic motility and phagocytic function.[23,24] We consider that these abovementioned mechanisms could explain why women with low levels of serum 25(OH) vitamin D are prone to recurrent UTIs. However, more studies are needed to investigate the mechanisms involved in the pathogenesis of vitamin D deficiency and predisposition to bacterial infections.

In case–control studies, Scholes et al.[25] and Hooten[26] reported that a history of UTI in the mother is associated with 2–3-fold increase in risk of UTI in her daughters. A maternal history of UTI suggests that inherited factors may be important in some cases of recurrent UTI.[27] Otherwise, this risk factor could reflect other shared environmental factors, or behaviors present in both mothers and daughters. The contribution of genetics to UTIs has been discussed in several studies.[28,29] Lundstedt et al. showed that susceptibility to acute pyelonephritis is inherited and that low CXCR1 expression might predispose to acute pyelonephritis.[29] In our study we found that a maternal history of UTI was associated with 1.6-fold increase in the risk of recurrent UTI.

Table 2
Results of the multivariate analysis of recurrent UTI among premenopausal women

Variable	OR (95% CI)	*p*-Value
Age >35 years	1.55 (1.10–2.82)	NS
Maternal history of recurrent UTI	1.60 (1.40–2.60)	0.05
No use of probiotics	1.94 (1.61–2.82)	0.04
25(OH) vitamin D of <15 ng/ml	4.0 (3.40–4.62)	0.001
Sexual intercourse ≥1 per week	1.25 (0.75–2.2)	NS

UTI, urinary tract infection; OR, odds ratio; CI, confidence interval; NS, not significant.

Lactobacilli are the dominant bacteria of the vaginal flora and possess antimicrobial properties that regulate the urogenital microbiota. Incomplete cure and recurrence of genitourinary infections leads to a shift in the local flora from a predominance of lactobacilli to coliform uropathogens. The use of Lactobacillus-containing probiotics to restore the commensal vaginal flora has been proposed for the treatment and prophylaxis of recurrent UTIs.[30] Recently, a meta-analysis was done regarding Lactobacillus for the prevention of UTIs in women.[31] Data from 127 patients in two studies were included. Results showed probiotic strains of Lactobacillus to be safe and effective in preventing recurrent UTIs in adult women. In our study we found no use of probiotics to be associated with recurrent UTIs in premenopausal women. However, more randomized clinical trials (RCTs) are needed to examine the efficacy of probiotics as prophylaxis in recurrent UTIs.

Our study has several limitations: being a retrospective study, including a relatively small number of subjects, having incomplete data concerning body mass index, and not investigating the role of vitamin D receptors, cathelicidin, and the innate immune system.

In conclusion, vitamin D deficiency was found to be associated with recurrent UTIs in premenopausal women. RCTs are needed to assess if a correction of serum levels of 25(OH) vitamin D could prevent the recurrence of UTIs.

Conflict of interest: The authors declare no conflicts of interest.

References

1. Foxman B, Brown P. Epidemiology of urinary tract infections: transmission and risk factors, incidence, and costs. *Infect Dis Clin North Am* 2003;**17**:227–41.
2. Foxman B, Gillespie B, Koopman J, Zhang L, Palin K, Tallman P, et al. Risk factors for second urinary tract infection among college women. *Am J Epidemiol* 2000;**151**:1194–205.
3. Schito GC, Naber KG, Botto H, Palou J, Mazzei T, Gualco L, et al. The ARESC study: an international survey on the antimicrobial resistance of pathogens involved in uncomplicated urinary tract infections. *Int J Antimicrob Agents* 2009;**34**:407–13.
4. Moreira JR, Siqueira IC, Alcantara AP, Guereiro De Moura CG, De Carvalho WA, Riley L. Antimicrobial resistance of *Escherichia coli* strains causing community-acquired urinary tract infections among insured and uninsured populations in a large urban center. *J Chemother* 2006;**18**:255–60.
5. Zhanel GG, Hisanaga TL, Laing NM, DeCorby MR, Nichol KA, Palatnik LP, et al. Antibiotic resistance in outpatient urinary isolates: final results from the North American Urinary Tract Infection Collaborative Alliance (NAUTICA). *Int J Antimicrob Agents* 2005;**26**:380–8.
6. Alos JI, Serrano MG, Gomez-Garces JL, Perianes J. Antibiotic resistance of *Escherichia coli* from community-acquired urinary tract infections in relation to demographic and clinical data. *Clin Microbiol Infect* 2005;**11**:199–203.
7. Karlowsky JA, Kelly LJ, Thornsberry C, Jones ME, Sahm DF. Trends in antimicrobial resistance among urinary tract infection isolates of *Escherichia coli* from female outpatients in the United States. *Antimicrob Agents Chemother* 2002;**46**:2540–5.
8. Holick MF. Vitamin D deficiency. *N Engl J Med* 2007;**357**:266–81.
9. Arnson Y, Amital H, Shoenfeld Y. Vitamin D and autoimmunity: new etiological and therapeutic consideration. *Ann Rheum Dis* 2007;**66**:1137–42.
10. Adams JS, Hewison M. Update in vitamin D. *J Clin Endocrinol Metab* 2010;**95**:471–8.
11. Nnoaham KE, Clarke A. Low serum vitamin D levels and tuberculosis: a systematic review and meta-analysis. *Int J Epidemiol* 2008;**37**:113–9.
12. Laaksi I, Ruohola JP, Tuohimaa P, Auvinen A, Haataja R, Pihalajamki H, et al. An association of serum vitamin D concentration < 40 nmol/L with acute respiratory tract infection in young Finnish men. *Am J Clin Nutr* 2007;**86**:714–7.
13. Nseir W, Taha H, Khateeb J, Grosovski M, Assy N. Fatty liver is associated with recurrent bacterial infections independent of metabolic syndrome. *Dig Dis Sci* 2011;**56**:3328–34.
14. Nseir W, Mograbi J, Abu-Rahmeh Z, Mahamid M, Abu-Elheja O, Shalata A. The association between vitamin D levels and recurrent group A streptococcal tonsillopharyngitis in adults. *Int J Infect Dis* 2012;**16**:735–8.
15. Mahamid M, Agbaria K, Mahamid A, Nseir W. Vitamin D linked to PFAPA syndrome. *Int J Pediatr Otorhinolaryngol* 2013;**77**:362–4.
16. Hooton TM, Stamm WE. Diagnosis and treatment of uncomplicated urinary tract infection. *Infect Dis Clin North Am* 1997;**11**:551–81.
17. O'Reilly M. Recurrent urinary tract infection. In: Stanton SL, Dwyer PL, editors. *Urinary tract infection in the female*. London: Martin Donitz; 2000. p. 227–40.
18. Raffi HS, Bates JM, Laszik Z, Kumar S. Tamm–Horsfall protein acts as a general host-defense factor against bacterial cystitis. *Am J Nephrol* 2005;**25**:570–8.
19. Chromek M, Slamova Z, Bergman P, Kovacs L, Podracka L, Ehren I, et al. The antimicrobial peptide cathelicidin protects the urinary tract against invasive bacterial infection. *Nat Med* 2006;**12**:636–41.
20. Chun RF, Adams JS, Hewison M. Back to the future: a new look at "old" vitamin D. *J Endocrinol* 2008;**198**:261–9.

21. Hertting O, Holm A, Luthje P, Brauner H, Dyrdak R, Jonasson AF, et al. Vitamin D induction of the human antimicrobial peptide cathelicidin in the urinary bladder. *PLoS One* 2010;**5**:e15580.
22. Wang TT, Nestel FP, Bourdeau V, Nagai Y, Wang Q, Liao J, et al. Cutting edge: 1,25-dihydroxyvitamin D3 is a direct inducer of antimicrobial peptide gene expression. *J Immunol* 2004;**173**:2909–12.
23. Bikle DD. Vitamin D and the immune system: role in protection against bacterial infection. *Curr Opin Nephrol Hypertens* 2008;**17**:348–52.
24. Lorente F, Fontan G, Jara P, Casas C, Garcia-Rodriguez MC, Ojeda JA. Defective neutrophil motility in hypovitaminosis D rickets. *Acta Paediatr Scand* 1976;**65**: 695–9.
25. Scholes D, Hooton TM, Roberts PL, Stapleton AE, Gupta K, Stamm WE. Risk factors for recurrent urinary tract infection in young women. *J Infect Dis* 2000;**182**:1177–82.
26. Hooton TM. Recurrent urinary tract infection in women. *Int J Antimicrob Agents* 2001;**17**:259–68.
27. Kunin CM. The natural history of recurrent bacteriuria in schoolgirls. *N Engl J Med* 1970;**282**:14443–8.
28. Svanborg-Eden C, Briles D, Hagberg L, McGhee J, Michalec S. Genetic factors in host resistance to urinary tract infection. *Infection* 1984;**12**:118–23.
29. Lundstedt AC, Leijonhufvud I, Ragnarsdottir B, Karpman D, Andersson B, Svanborg C. Inherited susceptibility to acute pyelonephritis: a family study of urinary tract infection. *J Infect Dis* 2007;**195**:1227–34.
30. Barrons R, Tassone D. Use of Lactobacillus probiotics for bacterial genitourinary infections in women: a review. *Clin Ther* 2008;**30**:453–68.
31. Grin PM, Kowalewska PM, Alhazzan W, Fox-Robichaud AE. Lactobacillus for preventing recurrent urinary tract infections in women: meta-analysis. *Can J Urol* 2013;**20**:6607–14.