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The Effect of Vitamin D Supplementation on Urinary Tract Infection Among Pregnant Patients in Mosul city

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ABSTRACT

Background: Urinary tract infection (UTI) remains an important disease and becomes more frequent in women in pregnancy. Due to the proximity of the highly colonized perineum, the urinary tract epithelium must be able to sense pathogens and elicit a fast innate immune response in order to keep its integrity. Vitamin D, apart from its well-known task to regulate calcium metabolism, has been recognized to influence innate and acquired immune reactions

Objective: 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 pregnant women in Mosul city.

Study method: a case control study. Setting: carried out at our private clinics for one year from March 2018 to March 2019. Patient and method: A case control study was carried out to one hundred thirty two pregnant patients and on same number of control pregnant women, all of them have UTI at our private clinics for about one year follow up. We handle the patients with a good history, examination, investigation, and treatment.

Results: Research study shows that there is evidence to support the positive effects of vitamin D on UTIs in the pregnant women.

Conclusion: In this case control study, we found that recurrent UTIs in pregnant women are associated with vitamin D deficiency.

Keywords: BMI (body mass index), UTI (urinary tract infection, E.coli (Escherechia coli), S aureus (Staph aureus), p mirabilis (proteus mirabilis),

INTRODUCTION

Urinary tract infections (UTIs) in pregnant women continue to pose a clinical problem and a great challenge for physicians. Although the incidence of bacteriuria in this population is only slightly higher than in non-pregnant women, its consequences for both the mother and the unborn child are more severe. There is a much higher risk (up to 40%) of progression to pyelonephritis, and possibly increased risk of pre-eclampsia, premature birth and low neonatal birth weight [1,2,3,4,5,6]. That is related to profound structural and functional urinary tract changes, typical for pregnancy. In about 80% of pregnant women dilation of the urinary tract combined with slight hydronephrosis is observed, caused partly by a reduction in smooth muscle tone with slowing of ureteral peristalsis, and partly by urethral sphincter relaxation. This may be due to high levels of circulating progesterone [1, 7]. Simultaneously, the enlarged uterus compresses the urinary bladder, thus increasing the intravesical pressure, which may result in vesico-ureteral reflux and urine retention in the bladder after miction, commonly observed in pregnant women. Urinary stasis and impairment of the physiological anti-reflux mechanism create conditions favorable for bacterial growth and ascending infection, so stasis of urine in the urinary tractwil predispose for occurrence and recurrence of UTI.

In the USA, and worldwide, uropathogens are increasingly resistant to antibiotics [.3,4,5,6,7] pregnant 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, 9, 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[13,14,15]. Vitamin D may have pleiotropic effects on various organ systems that are related to the distribution of the vitamin D receptor (VDR) throughout the body.[16] In addition to its effects on bone and mineral metabolism, vitamin D plays important roles in multiorgan systems, including the immune system. The VDR is expressed on monocytes and macrophages[17]. Moreover, vitamin D promotes macrophage maturation and the secretion of lysosomal enzyme and hydrogen peroxide, which participate in macrophages' antimicrobial activities[18]. Vitamin D stimulates antibacterial peptide expression in monocytes and macrophages, including cathelicidin and β-defensin, which are directly involved in killing intracellular bacteria.[19]In addition, vitamin D induces autophagy, an important process in the antibacterial response of macrophages to Mycobacterium tuberculosis.[20]. Hence, vitamin D deficiency might increase an individual's susceptibility to microbial infection. Indeed, previous studies have shown that vitamin D deficiency is associated with a higher risk of infection, especially respiratory tract infection[21,22].

Against this background, we conducted this case control study in order to examine whether there is any association between vitamin D and the risk of recurrent UTIs in pregnant women.

MATERIALS AND METHOD

Sample size and technique:

Five hundred pregnant patients were selected randomly for this study , after exposure to certain exclusion criteria , a total of 264 pregnant woman participants were randomly divided in to two groups, one of them received antibiotics with vitamin D 1,000 IU per day for one month , the other group received antibiotics only . If the participant was diagnosed with type II diabetes , or gestational diabetes at any time during the study, their involvement in the study ended.

Study design:

This was a retrospective study aimed at examining the association between serum vitamin D levels and recurrent UTIs in pregnant women. In order to assess this, we compared the two groups of pregnant women – with recurrent UTIs –one of the groups received antibiotics with vitamin D , the other received antibiotics only . diabetic patients had been excluded.

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 clinic, complete standard questionnaire at every visit concerning her medical condition, drug therapy, family history of different diseases, systemic bacterial infections, and results of laboratory analyses, including urinalysis and urine culture had been recorded ,ultrasonography for pregnancy and urinary tract . The results of chemistry analysis, including fasting blood glucose, serum calcium, and a complete blood count, were collected from the medical charts. Serum 25(OH) vitamin D levels were measured at the beginning of treatment for both experimental and control groups .also after one month of receiving 1000 IU vitamin D supplementation in experimental group. 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.

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.[23] 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.[24] 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.

RESULTS

Of 500 pregnant women ,264 only had met the inclusion criteria which were pregnant ladies at the second and third trimester with recurrent UTIs ,where 236 were excluded by exclusion criteria as following:(n=104) were in the first trimester, (n=27) had renal stones, (n=20) were type 2 diabetes mellitus, (n=5) had abnormal s.creatinine level , (n=10) developed gestational diabetes, (n=10) patients on steroid use,(n= 60) patient did not stick to follow up program.

Table 1: Distribution of vitamin D level among studied women with UTI in relation to the demographic characteristics.

Parameter	UTI and normal vit D (control)	UTI and abnormal vit. D (patient)	P-value
Age: **< 20 yrs.** **≥20 yrs.**	**70 (53%)** **62 (47%)**	**45 (34%)** **87 (66%)**	**0.001**
BMI: **≤ 18 Kg/m²** **18-25 Kg/m² ≥ 25 Kg/m²**	**17 (13%)** **74 (56%)** **41 (31%)**	**22 (17%)** **66 (50%)** **44 (33%)**	**0.6**
Rural **Urban**	**61 (46%)** **71 (54%)**	**42 (32%)** **90 (68%)**	**0.01**
Employer	**100 (76%)**	**86 (65%)**	**0.04**
Housewife	**32 (23%)**	**46 (35%)**	

There was statistically high significant difference between age of patients (P-value0.001) ,where patients over 20 years(87%) were more vulnerable to vitamin D deficiency than younger(45%).Also the BMI of patient statistics was not significant (P-value 0.6) ,where the BMI between 18-25 had the higher percentage(66%) of low vitamin D than those whom BMI below 18(22%) and those more than25 (44%). The patients from urban areas were more affected by vitamin D deficiency than patients from rural areas and the difference was significant (P-value 0.01).Regarding the employer patient from studied groups , (76%) in control group ,were better than the employers of experimental group (65%) . For housewives ,(23%) only were with normal vitamin D level , while (35%) were with abnormal serum vitamin D level . the difference was statistically significant (P-value<0.04).

Table 2: Categorization of s. vitamin D level among studied groups before and after vitamin D supplementation

Vitamin D classes		Experimental No. (%)	ControlNo. (%)	P-value
Before treatment				0.05
	Sufficient	35 (26.5%)	30 (22.7%)	
	Insufficient	14 (10.6%)	5 (3.8%)	
	Deficient	83 (62.9%)	97 (73.5%)	
After treatment				0.0001
	Sufficient	90 (68%)	28 (21%)	
	Insufficient	21 (16%)	61 (46%)	
	Deficient	21 (16%)	43 (33%)	

According to table (2) before treatment with vitamin D , the results of serum vitamin D level in the experimental and the control groups were as following:The percentage of deficient(<20ng/ml) vitamin D in both experimental and control groups were high 62.9% and73.5% respectively.Insufficient levels of vitamin D (20-30ng/ml) were 10.6% for experimental and 3.8% for control.Sufficient levels of vitamin D (30-50ng/ml) were 26.5% for experimental and 22.7% for control.The difference between both groups was not that highly significant (P-value<0.05).Where as in the groups after treatment by vitamin D 1000 IU for one month , the difference was highly significant (P-value<0.0001) , Regarding sufficient level , (68%)in experimental group and (21%) in control group.The insufficient level ,(16%) for experimental group and (46%) for control group. The deficiency of vitamin D was decreased significantly after treatment with vitamin D.The experimental group (16%) and (33%) in control group.So the doseof vitamin D used in treatment (1000 IU) is good for correction of deficiency status.

Table 3: Bacteriological findings in both study groups before and after treatment

Bacteriological finding		Pre-treatmentNo. (%)	Post-treatmentNo. (%)	P-value
Experimental				
	E coli	87 (65.91%)	32 (24.24%)	<0.05
	S aureus	23 (17.42%)	10 (7.58%)	<0.05
	P mirabilis	12 (9.09%)	6 (4.55%)	>0.05
	Mixed	10 (7.58%)	11 (8.33%)	>0.05
	Sterile	-	73 (55.30%)	<0.0001
Control				
	E coli	65 (49.24%)	43 (32.58%)	<0.05
	S aureus	32 (24.24%)	36 (27.27%)	>0.05
	P mirabilis	18 (13.64%)	13 (9.85%)	>0.05
	Mixed	17 (12.88%)	10 (7.58%)	>0.05
	Sterile	-	30 (22.73%)	<0.0001

In our study, we did culture of urine samples for both experimental group (the group of patients who receive vitamin D supplement 1000 IU for one month) and control group. The most common microorganism obtained from urine culture of both groups is *E.coli*. the antibiotics had been given according to sensitivity of micro organism(s) isolated. The results of experimental group in pre and post treatment (which was antibiotics only in control group and both antibiotics with vitamin D in experimental group) were as following:

For *E.coli* (65.9%) ,(24%) respectively ,P-value<0.05. *S.aureus*(17.4%),(7.6) P-value<0.05,P.mirabilis(9%),(4.5) P-value>0.05 mixed microorganisms(7.5%),(8.3%) P- value>0.05. While in 55.3% of patients post treatment by antibiotics and vitamin D , had sterile culture with very high significance (P-value 0.0001)

In control group, pre and post treatment the results were as following:

For E.coli (49%),(32.5%) respectively ,P-value<0.05. S. aureus (24%),(27%) P-value>0.05, P.mirabilis (13.6%),(9.8%) P-value>0.05mixed (12.8%),(7.5%) P-value>0.05.22.7% have sterile cultures after treatment with antibiotics only with P-value<0.0001.

Table 4: Statistical significance of Cure rate between experimental and control groups

Treatment outcome	Experimental No. (%)	Control No. (%)	P-value
Cured	89 (67.4%)	62 (47.0%)	0.001
Not cured	43 (32.6%)	70 (53.0%)	

(Table 4) Showed the net result of the study ,where the experimental group (received vitamin D supplement in addition to antibiotics) in comparison to control group, had a higher cure rate (67.4%) and (47%) respectively. Statistically, it's highly significant (P-value 0.001).

DISCUSSION

In this retrospective study, we found that vitamin D deficiency in pregnant 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.[23,24] Infections of the urinary tract induce epithelial cells to produce cathelicidin LL-37, protecting against bacterial infection.[25] Vitamin D is a potent stimulator of antimicrobial peptides including cathelicidin LL-37 in innate immunity.[26] 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.[27] 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.[28, 29] 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.[30] and Hooten[31] 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.[32] 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.[33, 34] Lundstedt et al. showed that susceptibility to acute pyelonephritis is inherited and that low CXCR1 expression might predispose to acute pyelonephritis.[35] In our study we found that a maternal history of UTI was associated with 1.6-fold increase in the risk of recurrent UTI.

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.[36] Recently, a meta-analysis was done regarding Lactobacillus for the prevention of UTIs in women.[37] 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 pregnant 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.

Recent studies indicate that the prevalence of serum 25(OH)D <30 nmol/L is high and worldwide in breastfeeding infants, and lack of sun exposure and vitamin D supplementation have been considered as contributing factors.[38,39] Breast milk may not provide enough vitamin D for infants, especially when the mothers are also vitamin D-deficient.[40,41] Due to insufficient exposure to sunlight and a diet not enriched with vitamin D, pregnant women suffer from vitamin D deficiency and lead often to birth of neonates with the same deficiency. [42] Therefore, additional vitamin D is needed from sunlight or vitamin D supplementation for both mothers and infants.

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

CONCLUSION

UTIs are one of the most common infections. Many pregnant women 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.

Although further research is needed, vitamin D can be part of the answer to individuals susceptible to UTIs and in pregnant patient populations who are at risk of recurrent UTI.

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