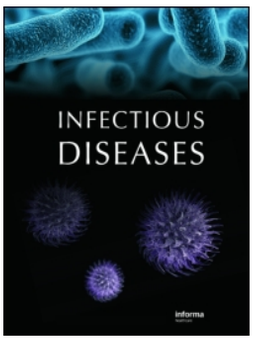

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ORIGINAL ARTICLE

# Prevention of urinary tract infections with vitamin D supplementation 20,000 IU per week for five years. Results from an RCT including 511 subjects

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**ABSTRACT**

**Background:** In observational studies vitamin D deficiency is associated with increased risk of infections, whereas the effect of vitamin D supplementation in randomized controlled trials is non-conclusive.

**Methods:** Five hundred and eleven subjects with prediabetes were randomized to vitamin $D_3$ (20,000 IU per week) versus placebo for five years. Every sixth month, a questionnaire on respiratory tract infections (RTI) (common cold, bronchitis, influenza) and urinary tract infection (UTI) was filled in.

**Results:** Mean baseline serum 25-hydroxyvitamin D (25(OH)D) level was 60 nmol/L. Two hundred and fifty-six subjects received vitamin D and 255 placebo. One hundred and sixteen subjects in the vitamin D and 111 in the placebo group completed the five-year study. Eighteen subjects in the vitamin D group and 34 subjects in the placebo group reported UTI during the study ($p < 0.02$), whereas no significant differences were seen for RTI. The effect on UTI was most pronounced in males. The effect of vitamin D on UTI was unrelated to baseline serum 25(OH)D level.

**Conclusion:** Supplementation with vitamin D might prevent UTI, but confirmatory studies are needed.

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Diabetes; respiratory infection; urinary tract infection; vitamin D



## Introduction

Vitamin D is vital for the calcium metabolism, and severe vitamin D deficiency leads to rickets in children and osteomalacia in adults. Vitamin D is produced in the skin upon UV exposure or obtained from the diet where fatty fish is the main source. For its activation, vitamin D is hydoxylated in the liver to 25-hydroxyvitamin D (25(OH)D), which is used as a marker of a subject's vitamin D status, and then in the kidneys (and some peripheral tissues) to the active form 1,25-dihydroxyvitamin D ($1,25(OH)_2D$).[1] The active form binds to the nuclear vitamin D receptor (VDR) which is located in tissues throughout the body, including immune cells,[2,3] and regulates transcription of hundreds of genes, including genes for antimicrobial peptides and cytokines.[4,5] Vitamin D is therefore likely to be important for more than bone health.

Thus, from observational studies there are a number of indications for an association between vitamin D deficiency and infectious diseases like tuberculosis, respiratory tract infections (RTI), influenza and sepsis.[6] As an example, non-pandemic influenza occurs mostly in temperate climates in the winter season when the serum 25(OH)D levels are low [7]; influenza pandemics are associated with solar activity cycles [8]; and even the mortality rates during influenza pandemics appear related to the level of solar radiation.[9] However, randomized controlled trials (RCT) with vitamin D supplementation for treatment and/or prevention of infections have so far not given conclusive results.[6]

We have recently performed a five-year intervention study with vitamin D in subjects with prediabetes for the prevention of progression to T2DM. As part of the study the subjects were asked every sixth month for upper respiratory infections (common cold, bronchitis, influenza) and urinary tract infections (UTI) since the last visit. We therefore had the opportunity to evaluate the effect of supplementation with vitamin D on these infections.

## Materials and methods

### *Study design*

The design of the study has been described in detail before.[10,11] In short, subjects with prediabetes (impaired fasting glucose (IFG) (serum glucose 6.0–6.9 mmol/L) and/or impaired glucose tolerance (IGT) (fasting serum glucose <7.0 mmol/L and 2-h value 7.8–11.0 mmol/L at oral glucose tolerance test (OGTT) with 75 g glucose) were included. Subjects with primary hyperparathyroidism, granulomatous disease, history of urolithiasis, cancer diagnosed in the past five years, unstable angina pectoris, myocardial infarction or stroke in the past year were excluded. Pregnant or lactating women, or women of fertile age with no use of contraception, were not included.

All visits were performed at the Clinical Research Unit at the University Hospital of North Norway. At the first visit, a brief

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clinical examination was performed, and questionnaires on medical history including infections, medication and vitamin D supplementation were filled in. Height and weight were measured wearing light clothing. Fasting blood samples had been collected at the OGTT, and supplementary non-fasting blood samples were drawn at this visit. The subjects were then randomized (non-stratified) in a 1:1 ratio to one capsule vitamin D (cholecalciferol 20,000 IU (Dekristol; Mibe, Jena, Germany)) per week or an identical looking placebo capsule containing arachis oil (Hasco-Lek, Wroclaw, Poland). New medication was supplied every sixth month and unused capsules returned and counted. The subjects were not allowed to take vitamin D supplements (including cod liver oil) exceeding 400 IU per day.

For the next five years, the subjects met every sixth month and filled in questionnaires on infections. Adverse events were specifically asked for. The questions regarding infections were:

- have you the last six months had a common cold, and in that case how many times?
- have you the last six months had bronchitis, and in that case how many times?
- have you the last six months had influenza or influenza-like illness (with fever), and in that case how many times?
- have you the last six months had a UTI, and in that case how many times?

If at the annual OGTT the fasting blood glucose was >6.9 mmol/L and/or the 2-h value >11.0 mmol/L the subject was considered to have T2DM, thus ending their participation in the study, and thereafter retested (if necessary) and followed by their general practitioner. Due to the inclusion of $HbA_{1c}$ (alone or in combination with glucose criteria) as a diagnostic criterion for diabetes in the WHO report from 2011,[12] and the acceptance of this in Norway the year later, it was also implemented in the present study from November 2012. Thus, if $HbA_{1c}$ alone was ≥6.5%, the subject was retested with new $HbA_{1c}$ measurement and if still ≥6.5% diagnosed as T2DM and ending their participation in the study. Also, if diagnosed elsewhere with T2DM between visits in the study, participation was ended.

Subjects who developed persistent hypercalcemia (serum calcium >2.55 mmol/L), and subjects who developed renal stones, or symptoms compatible with renal stones, were also excluded. In the initial protocol, subjects who during the study were diagnosed with cancer, coronary infarction, unstable angina pectoris, or stroke, were to be excluded from the study. From October 2011, this was changed to exclusion of subjects who during the study developed serious disease making it difficult or impossible to attend scheduled visits. As part of the safety monitoring, serum calcium was measured at each of the six-month visit.

Biochemical analyses including serum 25(OH)D were analyzed as previously described.[11]

### Statistical analyses

Normal distribution was evaluated with visual inspection of histograms and by kurtosis and skewness. Comparisons between the two groups at baseline and during the study were performed with Student's *t*-test or chi-square tests. Occurrence of RTI or UTI in the two groups was evaluated with Cox regression with gender and age as covariates.

$p < 0.05$ (two-tailed) was considered statically significant. Data are presented as mean ± SD for normally distributed values and as median (5th, 95th percentiles) for serum parathyroid hormone (PTH) that had a non-normal distribution. All statistical analyses were performed using IBM SPSS version 22 software (SPSS INC, Chicago, IL).

The power calculation of the study was made for the main endpoint (development of T2DM),[11] and a separate power calculation for the infection questionnaire was not made.

### Ethics

All subjects gave written informed consent. The study was approved by the Regional Committee for Medical and Health Research Ethics (REK NORD 81/2007) and by the Norwegian Medicines Agency (2007-002167-27). The trial is registered at ClinicalTrial.gov (NCT00685594).

## Results

Five hundred and eleven subjects were included in the study; 256 were randomized to vitamin D and 255 to placebo. Their baseline characteristics are shown in Table 1. The baseline serum 25(OH)D levels were 59.9 ± 21.9 nmol/L in the vitamin D group and 61.1 ± 21.2 nmol/L in the placebo group. During the intervention period, the mean serum 25(OH)D level in the vitamin D group increased to 110 nmol/L after 1 year and thereafter gradually to 122 nmol/L at the end of the study; whereas the levels remained stable in the placebo group. After 1 year median serum PTH decreased by 0.5 pmol/L in the vitamin D group, whereas there was an increase of 0.2 pmol/L in the placebo group ($p < 0.001$). A similar difference in serum PTH persisted throughout the study. The compliance rate was between 95 and 99% at all visits in both groups.

During the study, 50 subjects in the vitamin D group and 45 subjects in the placebo group dropped out or were excluded due to illness; and 103 subjects in the vitamin D group and 112 in the placebo group developed T2DM. The study flow including the number of subjects who attended the annual visits is shown in Figure 1. Regarding the main endpoint, development of T2DM, or the secondary endpoints (changes in measures of glucose metabolism and insulin resistance, serum lipids and blood pressure) there were no statistically significant differences between the two groups.[10,11]

No significant differences in adverse events were recorded as described in detail previously.[11] Regarding calcium-specific adverse events, two subjects in the vitamin D group and one subject in the placebo group developed renal stones and were excluded; one subject in the vitamin D group was excluded after a serum calcium of 2.64 mmol/L after six months with a retest value of 2.63 mmol/L (later testing showed normal serum calcium and PTH values), and two

Table 1. Baseline characteristics in the two study groups.

| | Vitamin D group ($n = 256$) | Placebo group ($n = 255$) |
|---|---|---|
| Male sex, *n* (%) | 161 (62.9) | 153 (60.0) |
| Age (years) | 62.3 ± 8.1 | 61.9 ± 9.2 |
| BMI (kg/m$^2$) | 30.1 ± 4.1 | 29.8 ± 4.4 |
| Current smokers, *n* (%) | 59 (23.0) | 47 (18.3) |
| Vitamin D supplement use[a] | 87 (34.0) | 92 (36.1) |
| Serum 25(OH)D (nmol/L) | 59.9 ± 21.9 | 61.1 ± 21.2 |
| Serum calcium (mmol/L) | 2.31 ± 0.08 | 2.31 ± 0.08 |
| Serum PTH (pmol/L) | 5.5 (3.4, 9.7) | 5.2 (3.1, 9.6) |
| Serum creatinine (μmol/L) | 69.7 ± 13.6 | 69.5 ± 13.9 |
| $HbA_{1c}$ (%) | 5.98 ± 0.28 | 5.97 ± 0.34 |
| Infections last six months | | |
| Common cold (yes/no) | 99/157 | 100/155 |
| Bronchitis (yes/no) | 7/249 | 13/242 |
| Influenza (yes/no) | 58/198 | 43/212 |
| UTI (yes/no) | 10/246 | 20/255 |

[a]Including cod liver oil.
BMI: body mass index; 25(OH)D: 25-hydroxyvitamin D; PTH: parathyroid hormone; $HbA_{1c}$: hemoglobin A1c; UTI: urinary tract infection.

subjects in the vitamin D group and one in the placebo group had single serum calcium values in the range 2.56–2.61 mmol/L that normalized at second testing, and thus continued in the study.

### Infections

At baseline, there were not any statistically significant differences between the groups regarding infections the previous six months, although there were considerably more subjects in the placebo than the vitamin D group who had experienced one or more UTI (20 subjects versus 10) (Table 1).

During the five-year intervention, a total number of 141 UTI events were recorded, 44 (18 incident and 26 recurrent) in the vitamin D group and 97 (34 incident and 63 recurrent) in the placebo group. The numbers of subjects who experienced one or more events with RTI or UTI are shown in Table 2. A statistically significant difference between the two groups was only seen for UTI, with less UTI in the vitamin D group. This difference was significant when evaluating subjects who experienced at least one UTI during the study period (18 in the vitamin D group vs. 34 in the placebo group, $p = 0.018$, Pearson's chi-square test); when also considering total number of UTI events ($p = 0.025$, chi-square test, linear-by-linear association), and when analyzing with Cox regression for first UTI event after inclusion in the study (HR 0.51; 95% CI 0.29–0.90, age and gender as covariates, $p = 0.021$) (Figure 2). The difference regarding UTI was statistically significant in men (3 in the vitamin D group vs. 11 in the placebo group) (HR 0.26; 95% CI 0.07–0.93, $p = 0.038$) (Figure 3), but did not reach statistical significance in women (15 in the vitamin D group vs. 23 in the placebo group) (HR 0.64; 95% CI 0.33–1.23, $p = 0.18$).

Although not statistically significant, there were more subjects with prior UTI in the placebo than the vitamin D group (20 subjects vs. 10 subjects). Since there is a high relapse rate for UTI, the lower rate of UTI in the vitamin D group during the study could therefore be due to this baseline difference. However, during the intervention, 7 of these 10 subjects in the vitamin D group and 7 of these 20 subjects in the placebo group had a recurrence during the study. Exclusion of these 30 subjects in the Cox regression therefore increased, and not diminished, the difference between the two groups regarding first UTI (HR 0.38; 95% CI 0.19–0.76), $p = 0.006$).

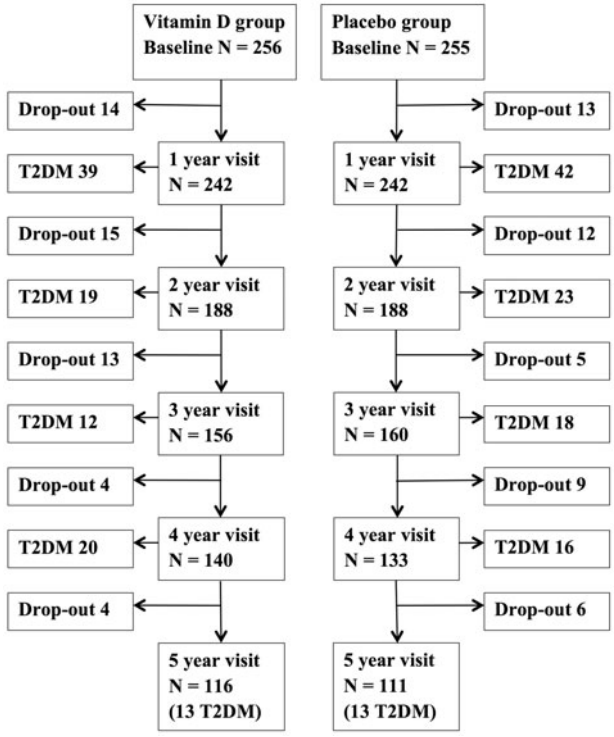


Figure 1. Flow chart of the study.

### Effect of baseline serum 25(OH)D

Baseline serum 25(OH)D levels did not differ significantly between those with or without an infection the previous six months (Table 3), nor was the baseline serum 25(OH)D level a significant predictor of infections during the intervention study in neither study group (data not shown).

In the group of subjects with serum 25(OH)D above 50 mnol/L at baseline (167 in the vitamin D group and 170 in the placebo groups) the effect of vitamin D supplementation regarding first UTI during the study was still significant (HR 0.49; 95% CI 0.25–0.96, $p = 0.038$). However, in the group of subjects with baseline serum 25(OH)D below 50 nmol/L (88 subjects in the vitamin D group and the 85 in the placebo group), the effect did not reach statistical significance (HR 0.53; 95% CI 0.17–1.64, $p = 0.27$).

## Discussion

In the present study, we have found supplementation with vitamin D to significantly reduce the occurrence and number of UTI during a five-year intervention study, whereas no effect was seen on RTI.

To our knowledge, this is the first RCT reporting effect of vitamin D on UTI. However, there are several observational reports linking vitamin D deficiency to UTI. Thus, in a case–control study by van der Starre et al., adult subjects with UTI

**Table 2.** Number of subjects according to number of events with common cold, bronchitis, influenza-like illness or urinary tract infection during the five-year study period.

| | Number of subjects | | | | | | | |
|---|---|---|---|---|---|---|---|---|
| | Common cold | | Bronchitis | | Influenza-like illness | | Urinary tract infection | |
| Number of events | Vitamin D | Placebo | Vitamin D | Placebo | Vitamin D | Placebo | Vitamin D | Placebo |
| 0 | 71 | 73 | 223 | 224 | 137 | 158 | 238 | 221 |
| 1 | 52 | 55 | 16 | 19 | 68 | 54 | 9 | 15 |
| 2 | 38 | 37 | 11 | 8 | 28 | 18 | 3 | 5 |
| 3 | 22 | 24 | 3 | 2 | 9 | 15 | 2 | 3 |
| 4 | 21 | 19 | 1 | 2 | 7 | 7 | | 5 |
| 5 | 17 | 10 | | | 4 | 2 | 3 | 1 |
| 6 | 12 | 11 | | | | 1 | | 1 |
| 7 | 11 | 7 | 1 | | 1 | | | 1 |
| 8 | 4 | 8 | 1 | | 2 | | 1 | |
| 9 | 1 | 1 | | | | | | |
| 10 | 2 | 3 | | | | | | 1 |
| >10 | 5 | 7 | | | | | | 2 |
| P vs. placebo (chi-square test) | ns | | ns | | ns | | 0.025 | |

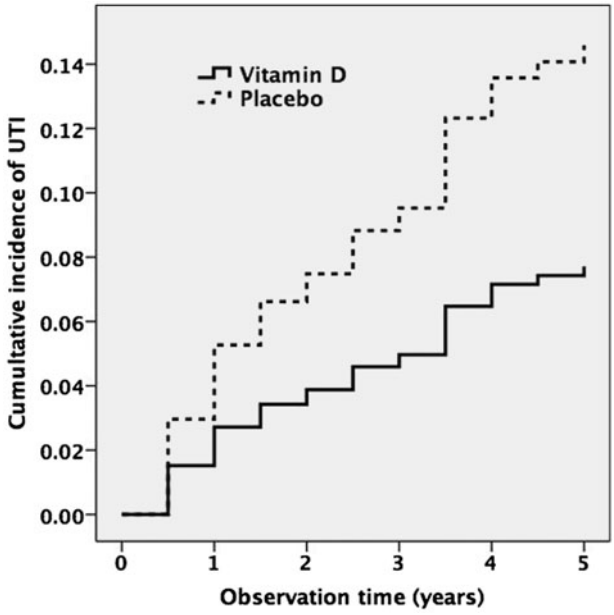


**Figure 2.** Cumulative probability of urinary tract infection (UTI) based on Cox regression with age and gender as covariates in the 256 subjects in the vitamin D group and the 255 subjects in the placebo group.

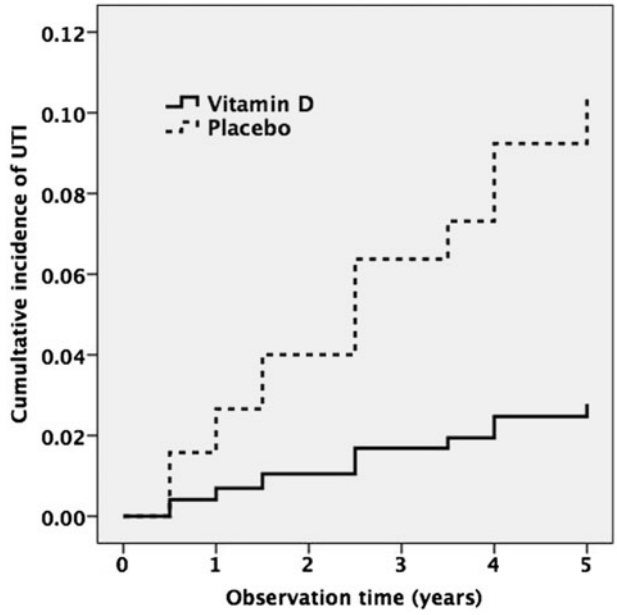


**Figure 3.** Cumulative probability of urinary tract infection (UTI) based on Cox regression with age as covariate in the 161 men in the vitamin D group and the 153 men in the placebo group.

had 28% lower serum 25(OH)D levels than controls [13]; in children with UTI Tekin et al. found the serum 25(OH)D levels to be approximately half those in the controls,[14] and a similar observation was made by Nesir et al. in premenopausl women [15]; Vaughan et al. found vitamin D deficiency to be associated with lower urinary tract symptoms in a cohort of 2387 men in the 2005–2006 NHANES [16]; Caretta et al. found low serum 25(OH)D levels to be associated with urinary tract symptoms and benign prostate hypertrophy in male subjects with T2DM [17]; and finally, Kwon et al. found vitamin D deficiency to be an independent risk factor for UTI after renal transplantation.[18]

There could be several mechanisms for a protective effect of vitamin D on UTI. It has been shown that vitamin D can induce production and secretion of the antimicrobial peptide cathelicidin by bladder epithelial cells [19,20]; vitamin D is important for innate immunity in defending against bacterial infections by increasing the neutrophilic motility and phagocytic function [21]; vitamin D supplementation could alter the chemical composition of the urine by increasing the urinary calcium excretion [22]; vitamin D has a direct effect on muscle function and could contribute to pelvic floor function and bladder emptying, particularly in women [23]; and in

**Table 3.** Baseline serum 25(OH)D levels in subjects with or without infection last six months before baseline.

| | Subjects with infection last six months | | Subjects without infection last six months | |
|---|---|---|---|---|
| | *N* | Serum 25(OH)D (nmol/L) | *N* | Serum 25(OH)D (nmol/L) |
| Common cold | 199 | 59.1 ± 21.0 | 312 | 61.4 ± 21.9 |
| Bronchitis | 20 | 52.9 ± 16.6 | 491 | 60.8 ± 21.7 |
| Influenza | 101 | 59.9 ± 20.8 | 410 | 60.6 ± 21.8 |
| UTI | 30 | 62.9 ± 24.1 | 481 | 60.3 ± 21.4 |
| All infections | 250 | 59.8 ± 21.8 | 261 | 61.2 ± 21.3 |

25(OH)D: 25-hydroxyvitamin D; UTI: urinary tract infection.

men, vitamin D appears to be a regulator of prostatic cell growth, could influence the development of benign prostatic hyperplasia (BPH), and thereby reduce the likelihood of UTI.[24]

The effect of vitamin D on BPH is supported by an observational study where subjects with the highest quintile of vitamin D intake had a 18% reduced risk of developing BPH compared to those in the lowest quintile [25]; and also from an RCT where the vitamin $D_3$ analog BXL628 was able to arrest prostate growth in subjects with moderate BPH.[26] In our study this is of particular interest since the effect of the vitamin D supplementation was particularly evident in men.

We did not observe any effect of vitamin D on the occurrence of RTI. This is in line with the conclusion in the recent review by Kearns et al. that included 13 RCTs with vitamin D for prevention of RTI.[6] Only two of those studies found a positive effect of vitamin D, whereas the other found no change in the incidence or severity of RTI or influenza symptoms.

Our study has two main weaknesses: we used questionnaires with self-reported occurrence of infections without any bacteriological, virological or serological verification, and the effect on infections was not a primary endpoint. It is also remarkable that the effect of vitamin D supplementation was not related to baseline serum 25(OH)D levels. Thus, the protective effect of vitamin D was significant not only in all subjects analyzed together, but also in those with baseline serum 25(OH)D above 50 nmol/L, a level that many consider as sufficient at least for bone health.[27] If our result is not a chance finding, this may indicate that the threshold for vitamin D effects is different for the urinary tract than for the skeleton.

Our study also have some strengths: the study was performed according to strict RCT rules, the questionnaire was administered and checked by highly trained nurses, we included a large number of subjects, and we gave sufficient vitamin D doses for a long period of time.

In conclusion, there is an abundance of observational studies regarding vitamin D and health effect, and for almost every disease examined, high serum 25(OH)D levels appear beneficial. However, RCTs with vitamin D supplementation have been disappointing.[28] In view of this, our result with a positive effect of vitamin D on UTI should be viewed with caution and more RCTs are clearly needed. In particular, the unexpected effect in subjects apparently vitamin D sufficient needs confirmation.

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## Disclosure statement

The authors do not have a commercial or other association that might pose a conflict of interest.

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