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Effect of vitamin D supplementation on health status in non-vitamin D deficient people with type 2 diabetes mellitus

S Westra¹, Y H M Krul-Poel¹, H J van Wijland², M M ter Wee³, F Stam¹, P Lips⁴, F Pouwer⁵ and S Simsek¹

¹Department of Internal Medicine, Medical Centre Alkmaar, Alkmaar, the Netherlands
²Department of General Practice, DIAZON, Alkmaar, the Netherlands
³Department of Epidemiology and Biostatistics, VU Medical Centre, Amsterdam, the Netherlands
⁴Department of Internal Medicine, Endocrine Section, VU Medical Centre, Amsterdam, the Netherlands
⁵Department of Medical and Clinical Psychology, Tilburg University, Tilburg, the Netherlands

Abstract

Objective: Increased levels of depressive symptoms, fatigue or pain (all dimensions of reduced health-related quality of life (HRQOL)) are common in people with type 2 diabetes mellitus (DM). Earlier studies have reported associations between low vitamin D status and fatigue and depressive symptoms. The aim of the present study was to examine the effects of vitamin D supplementation on dimensions of HRQOL in people with type 2 DM.

Design: Randomised, double-blind, placebo-controlled trial.

Methods: The effect of monthly cholecalciferol 50,000 IU vs placebo on HRQOL was assessed in 275 adults with type 2 DM derived from general practices. HRQOL at baseline and after six months using the Short Form 36 Health Survey (SF-36) was collected. Linear regression analyses were used to compare the change in HRQOL over time between the vitamin D and placebo group.

Results: 187/275 (68%) completed baseline and follow-up SF-36 and were included in the analysis. Median serum 25-hydroxyvitamin D almost doubled in the intervention group compared to that in the placebo group (58.5–106.0 nmol/L vs 60.0–61.5 nmol/L, respectively). A small significant difference (adjusted B: −8.90; 95% CI: −17.16 to −0.65) between both groups was seen concerning the SF-36 domain role limitations due to physical problems in disadvantage of the vitamin D group.

Conclusions: Six months of vitamin D supplementation did not improve HRQOL in non-vitamin D-deficient people with type 2 DM managed on oral antidiabetic therapy.

Introduction

With a total number of 415 million people in 2015, expecting to increase to a number of 642 million people in 2040, diabetes mellitus (DM) is a growing worldwide epidemic. It is common knowledge that people with DM are at increased risk for microvascular and macrovascular complications, including neuropathy, nephropathy, retinopathy, peripheral artery disease and cardiovascular disease (1). Furthermore, in people with type 2 diabetes mellitus (type 2 DM), relatively high prevalences of depression, fatigue and (neuropathic) pain were found...
resulting in a decreased quality of life (2, 3, 4, 5, 6). Depressive symptoms and fatigue in people with diabetes are related to an increased risk of developing diabetes-specific complications (2, 3). Moreover, people with depressive symptoms and diabetes had an almost 50% increased all-cause mortality rate, probably due to non-optimal self-care (2).

Low vitamin D status is common in people with type 2 DM (7), and previous observational studies demonstrated an association between low vitamin D status and a reduced health-related quality of life (HRQOL), fatigue and depressive symptoms (8, 9, 10, 11, 12, 13, 14). Two recent meta-analyses (15, 16) based on the results of randomised controlled trials, which investigated the effect of vitamin D supplementation on depressive symptoms, suggest an improvement of depressive symptoms after vitamin D supplementation (15, 16). Intervention studies concerning the effect of vitamin D supplementation on fatigue are scarce, and the studies that have been executed are difficult to compare as their research designs are very different. Lima and coworkers (17) performed a randomised placebo-controlled trial in adolescents and young adults with juvenile systemic lupus erythematosus and found a significant reduction of ‘fatigue-related to social life’ score (when using the Kids Fatigue Severity Scale) in the vitamin D group compared to placebo after 24 weeks of oral cholecalciferol 50,000IU per week (17). In addition, a significant improvement in fatigue score in all five scales (general, physical, emotional, mental and vigour) of the Multidimensional Fatigue Symptom Inventory Short Form was seen in primary care people with a low vitamin D status and fatigue as their main problem, after five weeks of vitamin D supplementation (oral ergocalciferol 50,000IU three times per week) (18). However, this study was not blinded or placebo-controlled. It should be noted that the majority of the people included in these studies did not have type 2 DM.

The biological mechanisms linking vitamin D status to HRQOL, depressive symptoms and fatigue in people with type 2 DM are not clear. Hypothetically, vitamin D deficiency may contribute to poor glycaemic control (19), which in turn leads to a higher risk to develop microvascular and macrovascular complications in the long term (19). Furthermore, due to the immunomodulatory properties of vitamin D and its association with oxidative stress, vitamin D may influence low-grade systemic inflammation, which is linked to both depressive symptoms and insulin resistance (20, 21). Another possible link between vitamin D status and depressive symptoms is an elevated parathyroid hormone (PTH) level that has been linked to depressive symptoms and insulin resistance and is increased in the state of vitamin D deficiency (22, 23). Moreover, vitamin D itself seems to have cardioprotective effects as well (24). Based on these findings, we hypothesise a positive effect of vitamin D supplementation on fatigue and depressive symptoms in people with type 2 DM. The aim of this study was to test whether six months of vitamin D supplementation improves the Short Form 36 (SF-36) Health Survey domain scores, especially the domains’ physical functioning, role limitations due to physical problems, social functioning, role limitations due to emotional problems, mental health and vitality, in people with type 2 DM, using a randomised double-blind placebo-controlled trial design.

Subjects and methods

Study design and patients

The SUNNY trial (acronym for StUdy the effect of vitamiN D supplemeNtation on glucaemic control in type 2 DM) is a double-blind randomised placebo-controlled clinical trial, with the primary aim to determine the effect of vitamin D supplementation on glycaemic control in people with type 2 DM (25). Secondary aim was to investigate whether vitamin D supplementation improved the dimensions of HRQOL (25). The trial was conducted in five general practices in and around the city of Alkmaar, the Netherlands, latitude 52°, between July 2012 and April 2013. Adult persons (≥18 years) with type 2 DM treated with lifestyle advice, metformin, and/or sulfonylurea derivatives (SU derivatives) were invited for participation in the study. Serum HbA1c had to be stable and below or equal to 8.0% (64mmol/mol) for the last three months without recent changes in hypoglycaemic agents. Main exclusion criteria were an impaired renal function (estimated glomerular filtration rate (eGFR) <30mL/min calculated from serum creatinine using the MDRD formula), any granuloma forming disorder, hypercalcaemia (serum calcium >2.65 nmol/L) of any reason, serum 25-hydroxyvitamin D (25(\(\text{OH}\))D) <15 nmol/L or >150 nmol/L, urolithiasis, psychiatric treatment for schizophrenia, organic mental disorder or bipolar disorder currently or in the past, insufficient knowledge of the Dutch language and substance abuse (other than nicotine) or no signed informed consent. Withdrawal criteria for premature termination of the trial were increase of HbA1c 69 mmol/mol (>8.5%),
hypotheses to cholecalciferol or placebo, onset of
urolithiasis, any change in antidiabetic medication or
serum 25(OH)D <15 or ≥250nmol/L, and during the study,
persons were not allowed to take vitamin D supplements.

This trial protocol was approved by the Medical
Ethics Committee of Noord-Holland, the Netherlands
and was conducted according to the principles of the
Declaration of Helsinki (NTR3154). A detailed description
of the protocol can be found elsewhere (25). Consent
of all participants was obtained after full explanation of
the purposes and nature of all procedures used in the
SUNNY trial.

**Intervention**

All participants were randomised according to either an
oral dose of cholecalciferol 50,000IU or an identically
looking placebo once a month for 6 months (Meander
Medical Center, Amersfoort, the Netherlands).

**Outcome measures**

Change in HRQOL after six months of vitamin D
supplementation was one of the secondary outcomes
described in the study protocol of the SUNNY trial (25).
HRQOL was assessed at baseline and six months after
baseline, using the Dutch version of the Short Form 36
(SF-36) Health Survey, which was translated and validated
by Aaronson and coworkers in 1994 (26). The SF-36
questionnaire is composed of 36 questions and represents
eight domains and two summary measures: physical
functioning, role limitations due to physical problems,
bodily pain, general health perceptions (together
presenting the physical component summary), mental
health, vitality, social functioning and role limitations
due to emotional problems (together presenting the
mental component summary). For each domain, scores
are summed and converted to a scale from 0 to 100, with
lower scores indicating a poorer HRQOL (27).

Demographic data, medical history, the use of
vitamin D supplements and diabetes-specific elements
(treatment, complications and duration) were collected
from medical records and during interviews. Lifestyle
information including smoking status (yes/no), alcohol
use (units per week), sun exposure (hours per week) and
physical activity (hours per week) were all self-reported
and gathered through interviews. Standard anthropometric
data (height and weight) and venous blood collection
were obtained from each person. Serum 25(OH)D was
measured using an iSYS automated immunoanalyzer
(IDS GmbH, Frankfurt, Germany). Data were collected at
baseline and after six months.

**Randomisation**

The participants were randomised 1:1 according to the
method of block randomisation with a block size of 10.
No stratification was used. The randomisation procedure
was performed by the pharmacist. The participants and
the research team remained blinded until the end of
the study.

**Statistical analysis**

People who completed the study (returned
questionnaires at baseline and 6 months) were included in the statistical
analyses. In case of one or two missing SF-36 domains,
linear imputation was used. When more SF-36 domains
were missing, the people were excluded. All data were
analysed using the Statistical Package of the Social
Sciences (SPSS software, version 20.0; SPSS Inc.). Baseline
characteristics were presented as means ± s.d., frequencies
(%) or as median (interquartile range (IQR)) in case of a
skewed distribution.

Linear regression analysis was used to assess the
mean difference between intervention and placebo
group after six months (mean difference reported as B
and β). Change in SF-36 domain score was analysed as
a dependent outcome with randomisation group as an
explanatory variable. To correct for regression to the
mean, all analyses were adjusted for its baseline value. In
case of skewed distribution, the separate SF-36 domains
were log transformed.

As we know that men and women provide different
outcome on the SF-36 questionnaire and oestrogen
use may increase the concentration of the vitamin
D-binding protein and improve hydroxylation of
vitamin D in the liver, the models will be tested for effect
modification by gender (26). Furthermore, all analyses
were corrected for confounding variables, which were
selected based on literature, including age, gender (if no
effect modification), BMI and season of blood collection.
Subgroup analyses were performed in people with low
vitamin D status, defined as 25(OH)D <50nmol/L
according to the practical guidelines of the Endocrine
Society and the Institute of Medicine.

A two-sided P value of <0.05 was considered as
significant.
Effect of vitamin D on HRQOL

Results

A total number of 787 people were screened for eligibility, of which 300 persons were recruited and
finally 275 persons (no show: n = 25) were randomised to either vitamin D supplementation (n = 136) or
placebo (n = 139) (Fig. 1). 487 (62%) people were
excluded from the study because they did not meet
the inclusion criteria (75%, mostly because they used
insulin) or refused to participate (25%). During the trial,
17 people met the withdrawal criteria for premature
termination due to change in antidiabetic medication
(n = 10), Hba1c >69 mmol/mol (>8.5%) (n = 5) or serum
25(OH)D <15 or >250 nmol/L (n = 2) and nine people
were lost to follow-up. SF-36 response rate at baseline
was 88% (241/275) and 89% at six months of follow-up
(191/215), total SF-36 response rate was 70% (191/275).
Linear imputation was executed in four people at
baseline and two people at follow-up for the SF-36
domains role limitations due to physical problems,
general health perceptions and role limitations due
to emotional problems. Four people were excluded
because information on two or more SF-36 domains
were missing, resulting in 187/275 (68%) people with
complete data.

Baseline demographic, clinical characteristics and
HRQOL of all people included in the vitamin D group
and in the placebo group are presented in Table 1. Mean
age was 68 years ± 8 and 67% of the people were men.
The median diabetes duration was 6 years (3–8) with a
median Hba1c of 51 (46–54 mmol/mol) (6.8 (6.4–7.1%)).
Overall mean serum 25(OH)D was 61.1 ± 22.6 nmol/L.

At baseline, 63 people (34%) had a serum 25(OH)D level
of 50 nmol/L or less; a serum 25(OH)D level between 50
and 75 nmol/L was present in 79 people (42%) and 45
people (24%) had a serum 25(OH)D >75 nmol/L. After
six months of vitamin D supplementation, the median
25(OH)D level almost doubled in the vitamin D group
from 58.5 (43.0–75.0) to 106.0 (85.0–117.0) nmol/L,
whereas in the placebo group, the 25(OH)D level
remained stable (serum 25(OH)D: 60.0 (44.0–74.0) to
61.5 (37.0–85.5) nmol/L). In the intervention group,
73% of the people achieved a serum 25(OH)D level
≥75 nmol/L at three months, and 84% after six months
of vitamin D supplementation. No differences in baseline
characteristics were seen between the people who were
randomised (n = 275) and those finally analysed (n = 187)
(data not shown).

Serum 25(OH)D and HRQOL

The present study revealed that vitamin D supplementation
did not affect HRQOL (Fig. 2 and Table 2) in people
with type 2 DM. No effect modification by gender was seen
(data not shown). A small significant difference, to the
detriment of the vitamin D group, was observed in the
SF-36 domain role limitations due to physical problems
(adjusted B: −8.90; 95% CI: −17.16 to −0.65).

In the group people with 25(OH)D <50 nmol/L (34%),
mean age was 67 years ± 8, 56% of the people were men
and mean serum 25(OH)D was 38 ± 8 nmol/L. Linear
regression revealed no differences in HRQOL between
the vitamin D and placebo group in this pre-specified
subgroup analysis (data not shown).
Table 1  Baseline demographic and clinical characteristics in the vitamin D group and the placebo group (n=187).

<table>
<thead>
<tr>
<th>Demographic parameters</th>
<th>Vitamin D group (n=94)</th>
<th>Placebo group (n=93)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (years)</td>
<td>67 ±8</td>
<td>68 ±9</td>
</tr>
<tr>
<td>Male</td>
<td>68 (72)</td>
<td>57 (61)</td>
</tr>
<tr>
<td>Diabetes duration (years)</td>
<td>6 (3–8)</td>
<td>6 (4–8)</td>
</tr>
<tr>
<td>White skin colour</td>
<td>91 (95)</td>
<td>90 (95)</td>
</tr>
<tr>
<td>Antidiabetic treatment</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Lifestyle adjustments</td>
<td>3 (3)</td>
<td>6 (7)</td>
</tr>
<tr>
<td>Metformin</td>
<td>66 (70)</td>
<td>48 (52)</td>
</tr>
<tr>
<td>SU derivatives</td>
<td>2 (2)</td>
<td>5 (5)</td>
</tr>
<tr>
<td>Metformin and SU derivatives</td>
<td>23 (25)</td>
<td>34 (37)</td>
</tr>
<tr>
<td>Microvascular complications* ≥ 1</td>
<td>25 (27)</td>
<td>13 (14)</td>
</tr>
<tr>
<td>Cardiovascular disease, yes</td>
<td>28 (30)</td>
<td>33 (36)</td>
</tr>
<tr>
<td>Single</td>
<td>8 (9)</td>
<td>20 (22)</td>
</tr>
<tr>
<td>Education level</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Low</td>
<td>63 (69)</td>
<td>64 (72)</td>
</tr>
<tr>
<td>Middle</td>
<td>21 (23)</td>
<td>18 (20)</td>
</tr>
<tr>
<td>High</td>
<td>7 (8)</td>
<td>8 (9)</td>
</tr>
<tr>
<td>Employment status</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Paid employment</td>
<td>24 (26)</td>
<td>25 (26)</td>
</tr>
<tr>
<td>Unemployed or incapacitated</td>
<td>8 (9)</td>
<td>7 (8)</td>
</tr>
<tr>
<td>Retired</td>
<td>62 (66)</td>
<td>61 (66)</td>
</tr>
<tr>
<td>Alcohol use &gt;2 units/day</td>
<td>12 (13)</td>
<td>12 (13)</td>
</tr>
<tr>
<td>Current smoker</td>
<td>15 (16)</td>
<td>13 (14)</td>
</tr>
<tr>
<td>Use of vitamin D supplements†</td>
<td>14 (15)</td>
<td>9 (10)</td>
</tr>
<tr>
<td>Physical activity</td>
<td></td>
<td></td>
</tr>
<tr>
<td>&lt;2 h/week</td>
<td>31 (33)</td>
<td>22 (24)</td>
</tr>
<tr>
<td>2–5 h/week</td>
<td>40 (43)</td>
<td>52 (56)</td>
</tr>
<tr>
<td>&gt;5 h/week</td>
<td>23 (25)</td>
<td>19 (20)</td>
</tr>
<tr>
<td>Sun exposure (%)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>&lt;5 h/week</td>
<td>34 (36)</td>
<td>37 (40)</td>
</tr>
<tr>
<td>5–10 h/week</td>
<td>46 (49)</td>
<td>44 (47)</td>
</tr>
<tr>
<td>&gt;10 h/week</td>
<td>14 (15)</td>
<td>12 (13)</td>
</tr>
<tr>
<td>Season of blood collection</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Spring</td>
<td>12 (13)</td>
<td>9 (9)</td>
</tr>
<tr>
<td>Summer</td>
<td>23 (25)</td>
<td>20 (22)</td>
</tr>
<tr>
<td>Autumn</td>
<td>43 (46)</td>
<td>49 (53)</td>
</tr>
<tr>
<td>Winter</td>
<td>16 (17)</td>
<td>16 (17)</td>
</tr>
<tr>
<td>Clinical characteristics</td>
<td></td>
<td></td>
</tr>
<tr>
<td>BMI (kg/m²)</td>
<td>27.7 (26.0–31.2)</td>
<td>27.5 (25.3–30.6)</td>
</tr>
<tr>
<td>HbA1c (mmol/mol)</td>
<td>51 (46–55)</td>
<td>51 (46–53)</td>
</tr>
<tr>
<td>HbA1c (%)</td>
<td>6.8 (6.4–7.2)</td>
<td>6.8 (6.4–7.0)</td>
</tr>
<tr>
<td>Serum 25(OH)D (nmol/L)</td>
<td>59.0 (43.0–75.0)</td>
<td>60.0 (44.0–74.0)</td>
</tr>
<tr>
<td>Serum PTH (pmol/L)</td>
<td>5.1 (3.8–6.8)</td>
<td>5.2 (4.0–6.5)</td>
</tr>
<tr>
<td>Health-related quality of life</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Physical functioning</td>
<td>85 (70–95)</td>
<td>85 (65–95)</td>
</tr>
<tr>
<td>Role limitations physical</td>
<td>100 (50–100)</td>
<td>100 (50–100)</td>
</tr>
<tr>
<td>Bodily pain</td>
<td>74 (52–100)</td>
<td>74 (62–100)</td>
</tr>
<tr>
<td>General health perceptions</td>
<td>67 (47–77)</td>
<td>62 (47–72)</td>
</tr>
<tr>
<td>Mental health</td>
<td>88 (76–92)</td>
<td>80 (64–92)</td>
</tr>
<tr>
<td>Role limitations emotional</td>
<td>100 (100–100)</td>
<td>100 (100–100)</td>
</tr>
<tr>
<td>Vitality</td>
<td>75 (60–85)</td>
<td>70 (55–85)</td>
</tr>
<tr>
<td>Social functioning</td>
<td>100 (88–100)</td>
<td>100 (75–100)</td>
</tr>
<tr>
<td>Physical component summary</td>
<td>80 (60–91)</td>
<td>76 (63–87)</td>
</tr>
<tr>
<td>Mental component summary</td>
<td>87 (74–91)</td>
<td>82 (70–90)</td>
</tr>
</tbody>
</table>

Continuous variables are presented in mean ± s.d. or median (IQR) depending on normality. Categorical variables are presented in numbers (%).

*Including retinopathy, nephropathy and neuropathy. †Maximum dose of 400 IU vitamin D supplement daily before the start of the trial.

25(OH)D, 25 hydroxyvitamin D; PTH, parathyroid hormone; SU derivatives, sulphonylurea derivatives.
Discussion

In this randomised, double-blind, placebo-controlled trial in Dutch people with well-controlled type 2 DM treated in general practice, we found a statistically significant decline (B: −8.90; 95% CI: −17.16 to −0.65) in the SF-36 domain ‘role limitations due to physical problems’ after six months of vitamin D supplementation. However, concerning the remaining SF-36 domains, no effect of vitamin D supplementation was found.

Before interpreting the results of our study, it should be emphasised that the SF-36 domain scores were not standardised, and they are calculated from different numbers of questions with different types of set response.
Table 2  Health-related quality of life (SF-36 domains) in the vitamin D group and the placebo group (n=187).

<table>
<thead>
<tr>
<th></th>
<th>Δ Vitamin D group (n=94)</th>
<th>Δ Placebo group (n=93)</th>
<th>β*</th>
<th>B*</th>
<th>95% CI</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>Physical functioning</td>
<td>−0.55 ± 12.77</td>
<td>1.21 ± 11.70</td>
<td>−0.62</td>
<td>−1.51</td>
<td>−4.99; 1.96</td>
<td>0.39</td>
</tr>
<tr>
<td>Role limitations physical</td>
<td>−5.32 ± 32.77</td>
<td>4.84 ± 32.61</td>
<td>−0.138</td>
<td>−8.9</td>
<td>−17.16; −0.65</td>
<td>0.04</td>
</tr>
<tr>
<td>Bodily pain</td>
<td>−0.24 ± 19.33</td>
<td>2.40 ± 16.59</td>
<td>−0.07</td>
<td>−2.52</td>
<td>−7.30; 2.27</td>
<td>0.3</td>
</tr>
<tr>
<td>General health perceptions</td>
<td>0.37 ± 13.39</td>
<td>3.10 ± 13.61</td>
<td>−0.063</td>
<td>−1.71</td>
<td>−5.54; 2.02</td>
<td>0.37</td>
</tr>
<tr>
<td>Mental health</td>
<td>−1.68 ± 11.78</td>
<td>−0.12 ± 13.09</td>
<td>−0.033</td>
<td>−0.83</td>
<td>−4.42; 2.77</td>
<td>0.65</td>
</tr>
<tr>
<td>Role limitations emotional</td>
<td>−3.72 ± 34.92</td>
<td>1.08 ± 33.50</td>
<td>−0.063</td>
<td>−4.31</td>
<td>−13.00; 4.37</td>
<td>0.31</td>
</tr>
<tr>
<td>Vitality</td>
<td>−2.71 ± 13.35</td>
<td>−1.00 ± 12.17</td>
<td>−0.064</td>
<td>−1.62</td>
<td>−5.11; 1.88</td>
<td>0.36</td>
</tr>
<tr>
<td>Social functioning†</td>
<td>0.00 (−12.50 to 0.00)</td>
<td>0.00 (−12.50 to 0.00)</td>
<td>0.95</td>
<td>0.95</td>
<td>0.80; 1.11</td>
<td>0.49</td>
</tr>
<tr>
<td>Physical component summary</td>
<td>−1.50 ± 13.82</td>
<td>2.89 ± 11.39</td>
<td>−0.15</td>
<td>−3.77</td>
<td>−7.26; −0.28</td>
<td>0.04</td>
</tr>
<tr>
<td>Mental component summary†</td>
<td>0.79 (−6.38 to 6.00)</td>
<td>0.00 (−4.50 to 7.50)</td>
<td>0.93</td>
<td>0.97</td>
<td>0.91; 1.04</td>
<td>0.34</td>
</tr>
</tbody>
</table>

A positive β value indicates an increase in the SF-36 domain in the vitamin D group compared to the placebo group.

*Adjusted for age, gender, BMI, baseline SF-36 domain, baseline 25-hydroxyvitamin and season of blood collection; †P<0.05; †Using log-transformed values; β of 0.95 (social functioning) indicating a 5% lower SF-36 score in the vitamin D group vs the placebo group after six months.

choices resulting in a fixed value per question, which is domain specific. Considering the SF-36 domain role limitations due to physical problems, which represent only four yes or no questions, thus valuing every question with twenty-five points, we interpret the statistically significant finding with a beta of only 0.138 (B: −8.90; 95% CI: −17.16 to −0.65) as clinically not relevant (27).

Other studies exploring the effect of vitamin D on HRQOL in people with diabetes are scarce. A recent systematic review from Hoffmann and coworkers (28), categorised fifteen articles (of which seven randomised placebo-controlled trials), which examined the effect of vitamin D supplementation on HRQOL according to length of intervention (more or less than six months) and study population (healthy vs diseased people; no studies focusing on diabetes were included). In contrast to our results, in four of the seven studies, which were derived from the group with diseased people and vitamin D intervention for six months or less, an improvement of HRQOL (especially in the domains role limitations due to physical problems, bodily pain, vitality and physical functioning; however, only two studies used (a variation of) the SF-36) after vitamin D supplementation was found, which was interpreted by the investigators as evidence for a small-to-moderate positive effect of short-term vitamin D supplementation on HRQOL in diseased people (28). However, no meta-analysis could be done due to the great heterogeneity in study samples, dose and type of vitamin D supplementation and the variation of HRQOL instruments that had been used. The before-mentioned study results should be viewed with caution as the quality of evidence is low due to poor methodological quality. Also, many of the differences in HRQOL that have been reported were small and not likely to be of value in the clinical setting. In addition, the only randomised placebo-controlled trial in this review with the maximal points for methodology, found no effect of vitamin D supplementation (daily oral 800IU vitamin D3) on the physical component summary or mental component summary in elderly people >70 years with previous low trauma osteoporotic fracture using the SF-12 (shortened version of the SF-36) after 24–62 months of follow-up (29).

Moreover, one recent double-blind, placebo-controlled study including 60 people receiving haemodialysis of whom 55% had a history of diabetes, did not demonstrate an effect of vitamin D supplementation (cholecalciferol 50,000IU/week for eight weeks followed by 50,000IU/month for four months) on HRQOL (using KDQOL-36, a kidney disease-specific measure of HRQOL including several parts of the SF-36 questionnaire) after six months of follow-up (30).

The main limitation of our study, which could explain that we found no positive effect of vitamin D supplementation on HRQOL in the present study, is the relatively good baseline HRQOL of several SF-36 domains in our study population that may have resulted in ceiling effects. In addition, the SF-36 domain scores in our study population are comparable with the SF-36 domain scores in the general Dutch population (26), suggesting low disease burden with few mental and physical limitations, leaving almost no opportunity for improvement. The low disease burden in our study population is also reflected in the small number of people with one or more than one microvascular complications (n=38, 20%) and the good glycaemic control with a median HbA1c of 51 (46–54) mmol/mol (6.8 (6.4–7.1%)).

Furthermore, when expecting a positive effect of vitamin D supplementation on HRQOL by reducing systemic low-grade inflammation or improving glycaemic
control leading to reduced or less severe diabetes-specific complications, the relatively short duration of the trial could be another reason for not finding an improvement of HRQOL after vitamin D supplementation.

Last, with a median 25(OH)D level of 58.5 nmol/L (43.0–75.0) in the vitamin D group at baseline, our subjects are already replete in vitamin D according to the current guidelines of the Institute of Medicine from 2011, which defines vitamin D deficiency as 25(OH)D <50 nmol/L in respect to bone health. However, Spedding and coworkers (31) suggested different 25(OH)D levels required for non-skeletal diseases and reported a minimum 25(OH)D level of 75 nmol/L for reducing depressive symptoms (level II evidence: randomised controlled trial) (31). With a median 25(OH)D level of 106.0 (85.0–117.0) in the vitamin D group at the end of the study, vitamin D intervention was effective to increase 25(OH)D concentration to a level of which an improvement in depressive symptoms could be expected. The strengths of our study are the randomised, double-blind, placebo-controlled design, the use of a well-validated questionnaire to determine HRQOL and the large study population.

In conclusion, six months of vitamin D supplementation did not improve HRQOL in people with tightly controlled type 2 DM derived from general practices. Longitudinal studies in people with poorly controlled type 2 DM, with multiple measurements over time concerning physical limitations, mental health and vitality and factors possible affecting these domains including low 25(OH)D level, inflammation factors, diabetes-specific treatment and complications and lifestyle factors are necessary to understand and eventually affect, the relationship between diabetes and a reduced (health-related) quality of life.

Declaration of interest
The authors declare that there is no conflict of interest that could be perceived as prejudicing the impartiality of the research reported.

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Author contribution statement
S S and Y K initiated the study. Y K and S W performed the data collection and statistical analyses together with M T W. S W wrote the manuscript and Y K edited the manuscript. S S first revised the paper critically. Thereafter, F S, H W, F P, M T W and P L revised the paper critically. S S is the guarantor of this work and, as such, had full access to all the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analyses. All the authors were involved in the final approval of the version to be published.

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