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Effect of vitamin D supplementation on health status in non-vitamin D deficient people with type ۲ diabetes mellitus.

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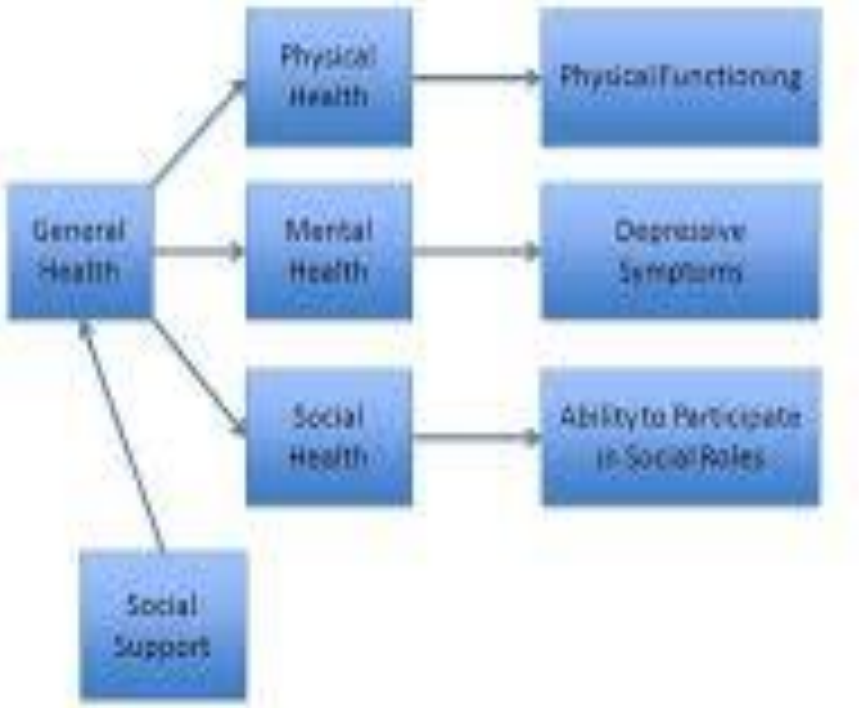
Introduction

Simplified HRQOL Framework



- With a total number of ٤١٥ million people in ٢٠١٥, expecting to increase to a number of ٦٤٢ million people in ٢٠٤٠, diabetes mellitus (DM) is a growing worldwide epidemic

•in people with type ٢ diabetes mellitus (type ٢ DM):

١.depression,

٢.fatigue and (neuropathic) pain were found resulting in a decreased quality of life .

. Depressive symptoms and fatigue in people with diabetes are related to an increased risk of developing diabetes-specific complications .

. Moreover, people with depressive symptoms and diabetes had an almost ٥٠% increased all-cause mortality rate, probably due to non-optimal self-care .

Low vitamin D status is common in people with type ٢ DM .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.

- The biological mechanisms linking vitamin D status to HRQOL, depressive symptoms and fatigue in people with type ٢ DM are not clear. Hypothetically, vitamin D deficiency may contribute to poor glycaemic control (١٩), which in turn leads to a higher risk to develop microvascular and macrovascular complications in the long term

Subjects and

methods

Study design and patients

- The SUNNY trial (acronym for StUdy the effect of vitamiN D supplemeNtation on glYcaemic control in type ٢ 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 ٢ DM.

Study design and patients

- 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 (NTR۳۱۵۴). A detailed description of the protocol can be found elsewhere (۲۵). 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 ٥٠,٠٠٠ IU or an identically looking placebo once a month for ٦ 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.
- HRQOL was assessed at baseline and six months after baseline, using the Dutch version of the Short Form ٣٦ (SF-٣٦) Health Survey, which was translated and validated by Aaronson and coworkers in ١٩٩٤.
- The SF-٣٦ questionnaire is composed of ٣٦ 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 ٠ to ١٠٠, with lower scores indicating a poorer HRQOL.

Outcome measures

- 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 self-reported and gathered through interviews. Standard anthropometric data (height and weight) and venous blood collection were obtained from each person.

Randomisation

- The participants were randomised ١:١ according to the method of block randomisation with a block size of ١٠. 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 ۶ months) were included in the statistical analyses.

Statistical analysis

- A two-sided *P* value of <٠,٠٥ was considered as significant.

Results

- A total number of ۷۸۷ people were screened for eligibility of which ۳۰۰ persons were recruited and finally ۲۷۵ persons (no show: *n* = ۲۵) were randomised to either vitamin D supplementation (*n* = ۱۳۶) or placebo (*n* = ۱۳۹) (Fig. ۱).
- ۴۸۷ (۶۲%) people were excluded from the study because they did not meet the inclusion criteria (۷۵%, mostly because they used insulin) or refused to participate (۲۵%).

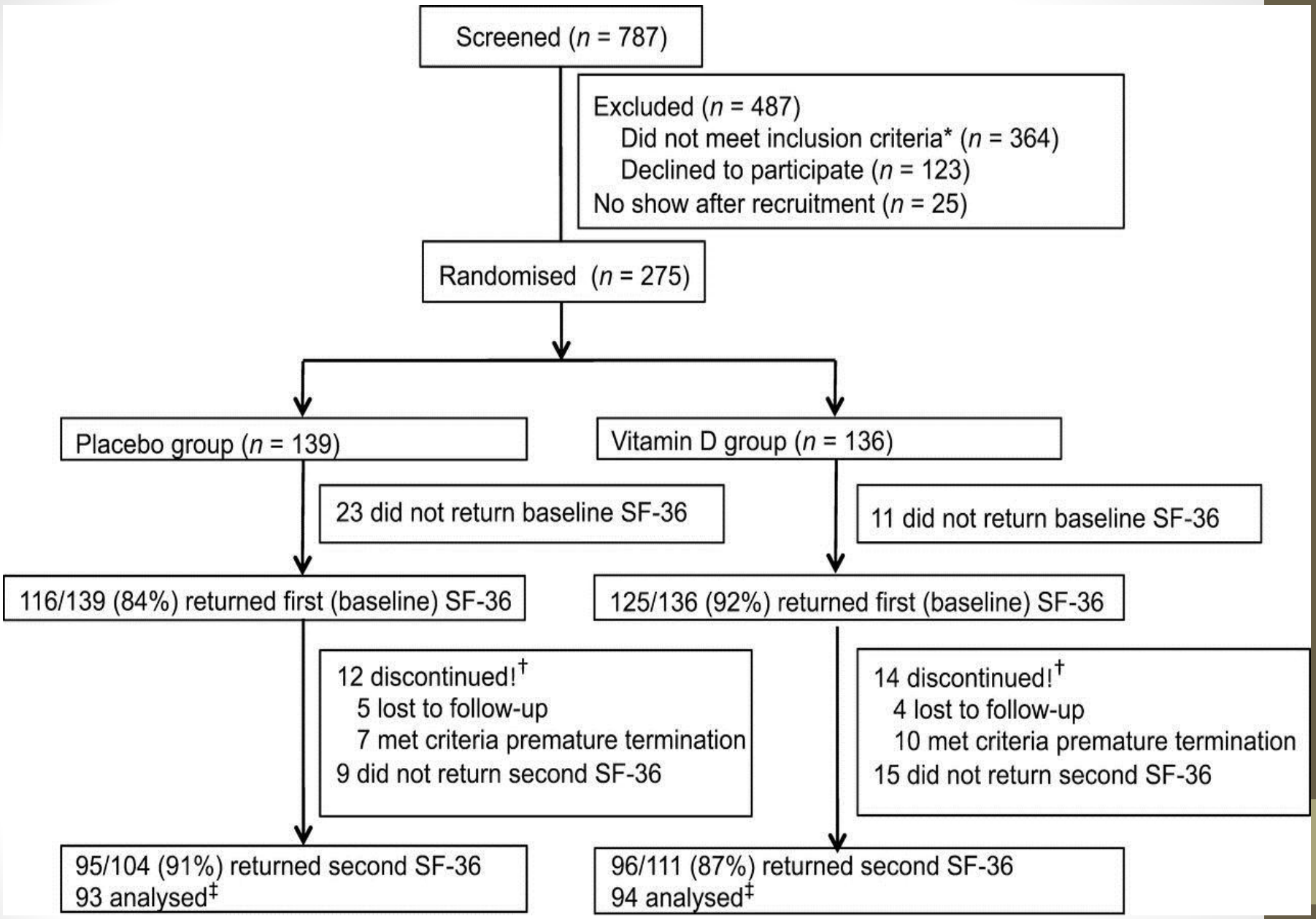

Screened (n = 787)
Excluded (n = 487)
Did not meet inclusion criteria* (n = 364)
Declined to participate (n = 123)
No show after recruitment (n = 25)
Randomised (n = 275)
Placebo group (n = 139)
Vitamin D group (n = 136)
23 did not return baseline SF-36
11 did not return baseline SF-36
116/139 (84%) returned first (baseline) SF-36
125/136 (92%) returned first (baseline) SF-36
12 discontinued!†
5 lost to follow-up
7 met criteria premature termination
9 did not return second SF-36
14 discontinued!†
4 lost to follow-up
10 met criteria premature termination
15 did not return second SF-36
95/104 (91%) returned second SF-36
93 analysed‡
96/111 (87%) returned second SF-36
94 analysed‡

Table ١
Baseline demographic and clinical characteristics in the vitamin D group and the placebo group (*n* = ١٨٧).

	Vitamin D group (*n* = ٩٤)	**Placebo group (*n* = ٩٣)**
Demographic parameters		
Age (years)	٦٧ ± ٨	٦٨ ± ٩
Male	٦٨ (٧٢)	٥٧ (٦١)
Diabetes duration (years)	٦ (٣–٨)	٦ (٤–٨)
White skin colour	٩١ (٩٥)	٩٠ (٩٥)
Antidiabetic treatment		
Lifestyle adjustments	٣ (٣)	٦ (٧)

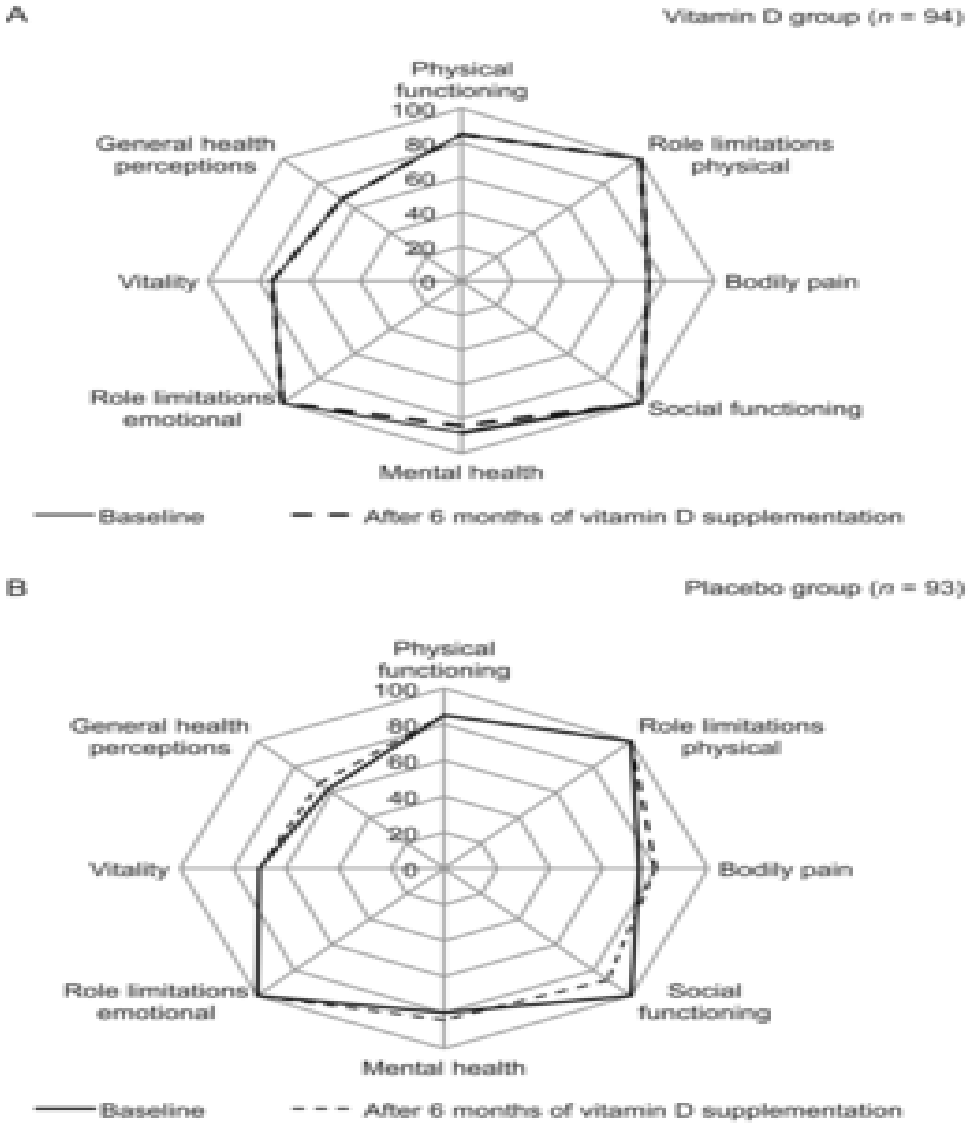
Clinical characteristics		
BMI (kg/m^2)	۲۷,۷ (۲۶,۰–۳۱,۲)	۲۷,۵ (۲۵,۳–۳۰,۶)
HbA$_{1c}$ (mmol/mol)	۵۱ (۴۶–۵۵)	۵۱ (۴۶–۵۳)
HbA$_{1c}$ (%)	۶,۸ (۶,۴–۷,۲)	۶,۸ (۶,۴–۷,۰)
Serum ۲۵(OH)D (nmol/L)	۵۹,۰ (۴۳,۰–۷۵,۰)	۶۰,۰ (۴۴,۰–۷۴,۰)
Serum PTH (pmol/L)	۵,۱ (۳,۸–۶,۸)	۵,۲ (۴,۰–۶,۵)
Health-related quality of life		
Physical functioning	۸۵ (۷۰–۹۵)	۸۵ (۶۵–۹۵)
Role limitations physical	۱۰۰ (۵۰–۱۰۰)	۱۰۰ (۵۰–۱۰۰)
Bodily pain	۷۴ (۵۲–۱۰۰)	۷۴ (۶۲–۱۰۰)
General health perceptions	۶۷ (۴۷–۷۷)	۶۲ (۴۷–۷۲)
Mental health	۸۸ (۷۶–۹۲)	۸۰ (۶۴–۹۲)
Role limitations emotional	۱۰۰ (۱۰۰–۱۰۰)	۱۰۰ (۱۰۰–۱۰۰)
Vitality	۷۵ (۶۰–۸۵)	۷۰ (۵۵–۸۵)
Social functioning	۱۰۰ (۸۸–۱۰۰)	۱۰۰ (۷۵–۱۰۰)
Physical component summary	۸۰ (۶۰–۹۱)	۷۶ (۶۳–۸۷)
Mental component summary	۸۷ (۷۴–۹۱)	۸۲ (۷۰–۹۰)

Serum ٢٥(OH)D and HRQOL

- The present study revealed that vitamin D supplementation did not affect HRQOL (Fig. ٢ and Table ٢) in people with type ٢ 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-٣٦ domain role limitations due to physical problems (adjusted B: –٨,٩٠; ٩٥% CI: –١٧,١٦ to –٠,٦٥).

Serum ۲۵(OH)D and HRQOL

- In the group people with ۲۵(OH)D <۵۰ nmol/L (۳۴%), mean age was ۶۷ years ± ۸, ۵۶% of the people were men and mean serum ۲۵(OH)D was ۳۸ ± ۸ 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).


A
Vitamin D group (n = 94)
Physical functioning
100
80
60
40
20
0
Role limitations physical
Bodily pain
Social functioning
Mental health
Role limitations emotional
Vitality
General health perceptions
Baseline
After 6 months of vitamin D supplementation
B
Placebo group (n = 93)
Physical functioning
100
80
60
40
20
0
Role limitations physical
Bodily pain
Social functioning
Mental health
Role limitations emotional
Vitality
General health perceptions
Baseline
After 6 months of vitamin D supplementation

Δ Vitamin D group (*n* = ۹۴)	Δ Placebo group (*n* = ۹۳)	*β**	*B**	۹۵% CI	*P*	
Physical functioning	−۰,۵۵ ± ۱۲,۷۷	۱,۲۱ ± ۱,۷۰	−۰,۰۶۲	−۱,۵۱	−۴,۹۹; ۱,۹۶	۰,۳۹
Role limitations physical	−۵,۳۲ ± ۳۲,۷۷	۴,۸۴ ± ۲,۶۱	−۰,۱۳۸	−۸,۹	−۱۷,۱۶; −۰,۶۵	۰,۰۴†
Bodily pain	−۰,۲۴ ± ۱۹,۳۳	۲,۴۰ ± ۶,۵۹	−۰,۰۷	−۲,۵۲	−۷,۳۰; ۲,۲۷	۰,۳
General health perceptions	۰,۳۷ ± ۱۳,۳۹	۳,۱۰ ± ۳,۶۱	−۰,۰۶۳	−۱,۷۱	−۵,۴۴; ۲,۰۲	۰,۳۷
Mental health	−۱,۶۸ ± ۱۱,۷۸	−۰,۱۲ ± ۱۳,۰۹	−۰,۰۳۳	−۰,۸۳	−۴,۴۲; ۲,۷۷	۰,۶۵
Role limitations emotional	−۳,۷۲ ± ۳۴,۹۲	۱,۰۸ ± ۳,۵۰	−۰,۰۶۳	−۴,۳۱	−۱۳,۰۰; ۴,۳۷	۰,۳۱
Vitality	−۲,۷۱ ± ۱۳,۳۵	−۱,۰۰ ± ۱۲,۱۷	−۰,۰۶۴	−۱,۶۲	−۵,۱۱; ۱,۸۸	۰,۳۶
Social functioning‡	۰,۰۰ (−۱۲,۵۰ to ۰,۰۰)	۰,۰۰ (−۱۲,۵۰ to ۰,۰۰)	۰,۹۵	۰,۹۵	۰,۸۰; ۱,۱۱	۰,۴۹
Physical component summary	−۱,۵۰ ± ۱۳,۸۲	۲,۸۹ ± ۱,۳۹	−۰,۱۵	−۳,۷۷	−۷,۲۶; −۰,۲۸	۰,۰۴†
Mental component summary‡	۰,۷۹ (−۶,۳۸ to ۶,۰۰)	۰,۰۰ (−۴,۵۰ to ۷,۵۰)	۰,۹۳	۰,۹۷	۰,۹۱; ۱,۰۴	۰,۳

Discussion

In this randomised, double-blind, placebo-controlled trial in Dutch people with well-controlled type ۲ DM treated in general practice, we found a statistically significant decline (B: –۸,۹۰; ۹۵% CI: –۱۷,۱۶ to –۰,۶۵) in the SF-۳۶ domain ‘role limitations due to physical problems’ after six months of vitamin D supplementation.

- 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-٣٦) after vitamin D supplementation was found, which was interpreted by the investigators as evidence for an small-to-moderate positive effect of short-term vitamin D supplementation on HRQOL in diseased people .

Moreover, one recent double-blind, placebo-controlled study including ۶۰ people receiving haemodialysis of whom ۵۵% had a history of diabetes, did not demonstrate an effect of vitamin D supplementation (cholecalciferol ۵۰,۰۰۰ IU/week for eight weeks followed by ۵۰,۰۰۰ IU/month for four months) on HRQOL (using KDQOL-۳۶, a kidney disease-specific measure of HRQOL including several parts of the SF-۳۶ questionnaire) after six months of follow-up .

- 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-۳۶ domains in our study population that may have resulted in ceiling effects.

- 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.

- 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 ٢ DM derived from general practices.


The End.