Vitamin D supplementation improves inflammation in type 2 diabetes patients: a systematic review and meta-analysis of randomized controlled trials

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Background

- Both vitamin D deficiency and systemic inflammation are common in type 2 diabetes.
- Vitamin D is proposed to have anti-inflammatory properties; however the effect of vitamin D supplementation on inflammation in type 2 diabetes has not been established.

Objective

- To conduct a systematic review and meta-analysis of randomized controlled trials (RCTs) examining the effect of vitamin D supplementation on inflammatory biomarkers in type 2 diabetes patients and to identify relevant knowledge gaps.

Methods

- Data Sources:** Medline, Medline-in-Process, EMBASE, CINAHL, all EBM were searched for studies up to 25 January 2017.

Selection Criteria:

- Studies:** RCTs and systematic reviews of RCTs

- Participants:** all participants with type 2 diabetes, for any duration, controlled or uncontrolled, with or without co-morbidities, and on any treatment regimen

- Interventions:** all doses, durations and types of vitamin D supplementation administered orally, intravenously, intramuscularly, or fortified in food

- Controls:** placebo, usual care or any pharmacological or non-pharmacological intervention

- Outcomes:** inflammatory biomarkers including adipokines

- No limits on setting or language

Data extraction and quality appraisal:

- Performed by two independent reviewers
- Risk of bias assigned as low, moderate, or high at the study-level
- Quality of the evidence was graded at the outcome-level using GRADE approach¹

Data synthesis:

- Random-effects models with results expressed as standardized mean differences (SMD) with 95% confidence intervals (95% CI)
- Sensitivity analysis to explore heterogeneity and risk of bias
- Meta-regression and subgroup analysis to explore potential confounders
- Funnel plots and Begg² and Egger³ tests to assess publication bias

Results

- 28 eligible RCTs (20 pooled in meta-analyses for C-reactive protein (CRP), tumor necrosis factor-alpha (TNF- α), interleukin-6 (IL-6), leptin, adiponectin, E-selectin, and erythrocyte sedimentation rate (ESR))

Table 1. Meta-analyses of effects of vitamin D supplementation on selected inflammatory markers

Pooled markers	Studies (n)	Sample (n)	SMD (95%CI)	P
CRP (mg/l)	15	978	-0.23 (-0.38, -0.09)	0.002
TNF- α (ng/l)	3	135	-0.49 (-0.84, -0.15)	0.005
Leptin (μ g/l)	3	107	0.42 (0.04, 0.81)	0.03
Adiponectin (μ g/l)	5	252	0.18 (-0.07, 0.43)	0.2
IL-6 (ng/l)	2	130	-0.37 (-0.82, 0.07)	0.1
ESR (mm/hr)	2	90	-0.47 (-0.89, -0.05)	0.03
E-selectin (ng/ml)	2	164	-0.37 (-0.82, 0.07)	0.9

CRP: meta-analysis of vitamin D versus placebo/ usual care

TNF- α : meta-analysis of vitamin D versus placebo

ESR: meta-analysis of vitamin D vs placebo/usual care

Leptin: meta-analysis of vitamin D vs placebo

Summary of Main Findings

- We found significant differences between vitamin D and placebo groups for CRP, TNF- α , leptin, and ESR, but not for adiponectin, IL-6, or E-selectin (Table 1).
- Most studies were low to moderate risk of bias with low heterogeneity (I^2 0-38%; P_{het} > 0.1).
- Differences in CRP remained significant in a sensitivity analysis limited to only low risk of bias studies (p =0.04); however differences for TNF- α and leptin were attenuated (both p >0.05).

Quality and Exploratory Analyses

- Quality of the evidence was deemed high for CRP and adiponectin, moderate for leptin, and low for TNF- α , IL-6, E-selectin and ESR.
- Exploratory analyses were only possible for CRP, TNF- α , leptin, and adiponectin (n >2).
- We found no influence for dose or duration of supplementation or of baseline sample characteristics including age, sex, body mass index, diabetes duration, or baseline 25-hydroxyvitamin D levels.
- Visual inspection of funnel plots and Begg's and Egger's tests showed no evidence of publication bias for CRP, TNF- α , leptin, or adiponectin.

Conclusions

- We provide level-one evidence of beneficial effects of vitamin D supplementation on inflammation in type 2 diabetes.
- Larger and longer-term RCTs are needed to establish whether improved inflammation following vitamin D supplementation translates into better health outcomes for type 2 diabetes patients.

References

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