Vitamin D status and weight loss: a systematic review and meta-analysis of randomized and nonrandomized controlled weight-loss trials

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ABSTRACT
Background: Obesity is associated with lower concentrations of serum 25-hydroxyvitamin D; however, uncertainty exists as to the direction of causation. To date, meta-analyses of randomized controlled vitamin D-supplementation trials have shown no effect of raising circulating vitamin D on body weight, although several weight-loss-intervention trials have reported an increase in circulating vitamin D after weight reduction.

Objective: We undertook a systematic review and meta-analysis of randomized and nonrandomized controlled trials to determine whether weight loss compared with weight maintenance leads to an increase in serum 25-hydroxyvitamin D.

Design: A systematic search for controlled weight-loss-intervention studies published up to 31 March 2016 was performed. Studies that included participants of any age with changes in adiposity and serum 25-hydroxyvitamin D as primary or secondary outcomes were considered eligible.

Results: We identified 4 randomized controlled trials (n = 2554) and 11 nonrandomized controlled trials (n = 917) for inclusion in the meta-analysis. Random assignment to weight loss compared with weight maintenance resulted in a greater increase in serum 25-hydroxyvitamin D with weight maintenance than weight loss. The mean difference of 2.59 nmol/L (95% CI: 1.38, 4.84 nmol/L) was observed in nonrandomized trials. No evidence for a dose-response effect of weight loss on the change in serum 25-hydroxyvitamin D was shown overall.

Conclusions: Our results indicate that vitamin D status may be marginally improved with weight loss in comparison with weight maintenance under similar conditions of supplemental vitamin D intake. Although additional studies in unsupplemented individuals are needed to confirm these findings, our results support the view that the association between obesity and lower serum 25-hydroxyvitamin D may be due to reversed causation with increased adiposity leading to suboptimal concentrations of circulating vitamin D. This trial was registered at www.crd.york.ac.uk/PROSPERO/ as CRD42015023836.

Keywords: meta-analysis, obesity, serum 25-hydroxyvitamin D, vitamin D, weight loss

INTRODUCTION

Obesity and its related diseases are responsible for an ever-mounting burden of morbidity and mortality worldwide. Obesity and vitamin D deficiency often coexist, which has led some researchers to question whether the relation is causal. If raising circulating vitamin D concentrations reduces body weight, vitamin D supplementation would offer immense potential as an inexpensive and safe treatment of obesity in the context of this global epidemic.

Despite the observational association between lower serum 25-hydroxyvitamin D (25(OH)D) concentrations and higher body weight, in meta-analyses of randomized controlled trials (RCTs), vitamin D supplementation has been largely ineffective for treating obesity (3, 4) or improving cardiovascular or metabolic outcomes (5–7). In addition, in several Mendelian randomization studies, it has been reported that genetic variants that confer low 25(OH)D status are not related to higher BMI (in kg/m²) (8) or risk of type 2 diabetes (9) or other cardiometabolic diseases (10). This apparent inconsistency may be explained by reverse causation with higher body weight resulting in lower serum 25(OH)D concentrations. Both volumetric dilution (11) and a greater sequestration (12) of fat-soluble vitamin D by increased quantities of body fat have been hypothesized to contribute to the lower circulating vitamin D observed in obesity. Indeed, in several animal and human studies, weight loss (13, 14), fasting (15, 16), and exercise (17) have been associated with a subsequent increase in serum 25(OH)D concentrations, which may have been attributable to the release of vitamin D from adipose tissue during the turnover of triglycerides for fuel (16) or the change in volume of fat mass (11).

The purpose of this systematic review was to determine, with the use of meta-analysis of randomized and nonrandomized controlled weight-loss trials, whether weight loss compared with...
weight maintenance in humans raises serum 25(OH)D. We hypothesized that, if adipose tissue releases vitamin D during lipid mobilization, the amount of weight lost would be proportional to the increase in circulating 25(OH)D, and thus with the use of meta-regression we further investigated whether a dose-response relation between a weight change and serum 25(OH)D exists.

METHODS

This systematic review with a meta-analysis was registered, and its protocol published at the PROSPERO International Prospective Register of Systematic Reviews (www.crd.york.ac.uk/PROSPERO/; CRD42015023836). We conducted the review according to the Preferred Reporting Items for Systematic Reviews and Meta-Analyses statement (18) and the Meta-analysis of Observational Studies in Epidemiology group checklist (19).

Search strategy

Electronic databases including Ovid Medline (wwwovidsp.ovid.com), Embase (www.embase.com), the Cumulative Index to Nursing and Allied Health (www.health.ebsco.com/products/tecinarhl-database), Scopus (www.scopus.com), and the Web of Science (www.thewebofknowledge.com) were systematically searched to identify relevant studies that were published in English up to 21 November 2014, and a further-updated search was performed to identify new studies that were published up to 31 March 2016. With previous experience in library work, SRM developed the systematic literature search strategies (OVID Medline and Embase search strategies are presented in Supplemental Material Search Strategy). Hand searching of meta-analyses and reviews and cited reference searching of identified studies in the Web of Science was also performed to search for studies that might have been missed.

Study selection

The initial screening of titles and abstracts for eligibility was performed by one researcher (SRM). Ten percent (10%) of identified reports were randomly selected for screening by a second independent researcher (ASH) with an acceptable agreement rate specified as ≤5%. If the relevance of the article could not be determined by title and abstract screening alone, the full text was retrieved for screening. Conference proceedings and studies that were only published in abstract form were not considered eligible. Controlled weight-loss–intervention studies, including hypocaloric dietary interventions, exercise interventions, or combinations thereof, were considered for inclusion if they provided data on 1) preintervention and postintervention serum 25(OH)D concentrations as either a primary or secondary outcome and 2) the weight change or other suitable measures of change in adiposity as either a primary or secondary outcome. Pharmacologic weight-loss–intervention studies were not considered eligible for inclusion because of the unknown effects of pharmacologic agents on vitamin D status. No restrictions were placed on participant characteristics such as age, ethnicity, body habitus, or health status. If the study included vitamin D supplementation, weight-loss and weight-maintenance groups were required to have matching supplemental vitamin D intakes to reduce the potential for confounding. Studies that were identified as potentially relevant but did not meet the inclusion criteria were recorded along with their reasons for exclusion.

Data extraction

All relevant articles that were deemed to meet the inclusion criteria underwent a duplicate data extraction by 2 independent researchers (SRM and ASH) with the use of extraction forms developed for the study. For factorial studies, data from each intervention arm that met the inclusion criteria were extracted. Data from separate arms were combined for a quantitative meta-analysis according to whether participants were in weight-loss or weight-maintenance groups to provide a single pairwise comparison for each trial (20). The uniqueness of 2 studies (21, 22) was clarified with one author.

Because of the limited half-life of serum 25(OH)D (23) and greater initial weight loss (24), we hypothesized that any effect of weight loss on circulating vitamin D would be observed soon after onset of the weight-loss intervention. Therefore, data from initial follow-up visits were extracted. The reported change in serum 25(OH)D was extracted directly, or preintervention and postintervention serum 25(OH)D concentrations were used to determine the change in serum 25(OH)D. The SE or SD of the mean change in 25(OH)D was extracted directly or was calculated from preintervention and postintervention SDs with the use of correlation coefficients that were derived from other identified studies at similar time points (20). Serum 25(OH)D was converted to nanomoles per liter if it was reported as nanograms per milliliter by multiplying by a factor of 2.496 (25). The reported mean changes in measures of adiposity at the corresponding follow-up visit were extracted directly, or preintervention and postintervention measures were used to determine the changes. When an adiposity measure such as the percentage of body fat or BMI was not reported directly, it was calculated from the provided data when possible.

Daily supplemental intake of vitamin D was recorded as international units per day [1 IU vitamin D = 0.025 μg vitamin D (26)]. An author of one study (27) was contacted to ascertain supplemental vitamin D intake. Group- and study-level data were collected on the several other variables as follows: baseline BMI, age, and serum 25(OH)D; seasonal influence (increasing or decreasing UVB exposure during follow-up); sex (percentage of women); the serum 25(OH)D analysis methodology, quality control, and CVs; and latitude.

Quality assessment

All included studies were assessed for risk of bias by 2 independent investigators (SRM and ASH) with the use of bias-analysis forms that were developed for the study. Cochrane criteria (20), including the sequence generation, allocation concealment, blinding of participants and outcome assessors, incomplete outcome data, and selective outcome reporting, were used to summarize the quality of trials in which participants were randomly assigned to weight loss or weight maintenance. Risk of Bias Assessment Tool for Nonrandomized Studies criteria (28), including the selection of participants, study-specific confounding variables (i.e., change of season and supplemental vitamin D intake), measurement of exposure, blinding of outcome assessments, incomplete outcome data, and selective
outcome reporting, were used to summarize the quality of nonrandomized trials included in the meta-analysis. RevMan 5.3 software (The Cochrane Collaboration, The Nordic Cochrane Centre) was used to generate summary bias-analysis figures. We evaluated the overall quality of the evidence produced in the meta-analysis according to the grading of recommendations assessment, development, and evaluation criteria (29) for high risk of bias, imprecision, indirectness, heterogeneity, and publication bias with the use of GRADEpro 2015 software (Evidence Prime Inc., McMaster University).

Statistical methods

The primary outcome measure was the weighted mean difference (WMD) in the change in serum 25(OH)D (nmol/L) from baseline to follow-up between groups who were randomly assigned to weight loss or weight maintenance. The secondary outcome measures were the WMD in the change in serum 25(OH)D (nmol/L) from baseline to follow-up between weight-loss and weight-maintenance groups in nonrandomized weight-loss–intervention studies and the overall WMD of both randomized and nonrandomized studies. A random-effects meta-analysis was used to estimate effect estimates because of underlying differences in study designs and methodologies (20).

We assessed risk of publication bias overall by evaluating a funnel plot, including for asymmetry, and assessed risk of small study bias with the use of Egger’s test whereby, in the presence of bias, $P$ values were <0.05 (30). The between-study heterogeneity was assessed with the use of the $I^2$ statistic (20). Sensitivity to influential studies was assessed by withholding studies individually from the model. Sensitivity analyses were also conducted on the basis of reported vitamin D supplementation, season, influence, the percentage of women, serum 25(OH)D analysis methodology and highest reported CV, baseline age and serum 25(OH)D, duration of the study, and intervention type. A random-effects weighted meta-regression was used to test for a dose-response effect of a reduction in adiposity on the WMD in serum 25(OH)D for adiposity outcomes with $\geq 10$ contributing studies (31). All statistical analyses were conducted in Stata 11.2 software (StataCorp LP), and a 2-sided 0.05 level of significance was used in all cases.

RESULTS

A total of 6794 records were identified for potential inclusion from the following databases that were current to 21 November 2014: OVID Medline, $n = 1037$; Embase, $n = 2120$; Cumulative Index to Nursing and Allied Health Literature, $n = 415$; Scopus, $n = 1995$; and Web of Science, $n = 1227$ (Figure 1). After de-duplication, 4667 unique records remained, and the updated search, which was current to 31 March 2016, and hand searching yielded 418 additional unique records. Twenty-six full-text articles were assessed for eligibility, of which 11 articles were excluded (Supplemental Table 1). Of the 15 articles that met our inclusion criteria (Table 1), 4 articles were RCTs ($n = 2554$ individuals) (13, 14, 32, 33), and 11 articles were nonrandomized trials ($n = 917$ individuals) (21, 22, 27, 34–41). All 15 weight-loss interventions used caloric restriction, and 7 interventions also included exercise components. The median time to first follow-up was 26 wk (IQR: 26–52 wk). Information on supplemental vitamin D intakes was available for all but one study (14) with a median intake of 350 IU/d (95% CI: 0–1000 IU/d) across all other trials. Serum 25(OH)D was analyzed with the use of a variety of methods including radioimmunoassay (Dia-Sorin) ($n = 10$ studies) (13, 21, 22, 32, 34, 36, 37, 39–41), liquid chromatography–tandem mass spectrometry ($n = 2$ studies) (14, 33), chemiluminescence immunoassay ($n = 2$ studies) (35, 38), and electrochemiluminescence immunoassay ($n = 1$ study) (27). Two studies reported participation in external serum 25(OH)D quality-assurance programs (14, 40), and reported CVs ranged from 6.7% to 21.4%. Overall, the median change in weight in the intervention group was a loss of 6.8 kg (IQR: −5.3 to −8.4 kg) compared with a median loss of 0.1 kg (IQR: −0.6 to 0.3 kg) in the control group. The median change in serum 25(OH)D was an increase of 7.2 nmol/L (IQR: 5.8–9.9 nmol/L) in the intervention group, whereas a median increase of 3.6 nmol/L (IQR: 0.7–6.0 nmol/L) was observed in the control group.

Study quality

Few ($n = 4$ studies) RCTs that met our inclusion criteria for meta-analysis were identified, and only one of these RCTs specified the methods of allocation concealment (Supplemental Figures 1 and 2). One RCT (14) did not record nonstudy supplemental vitamin D intake, but because the participants were randomly assigned and had similar baseline dietary supplement use (55% of participants in the intervention group compared with 52% of participants in the control group), we made the assumption that this intake would have been similar between groups. Authors who reported on non-RCTs often reclassified participants who did not meet their assigned weight-loss goals as being in the weight-maintenance group ($n = 6$ studies), and in some studies, participants were recruited separately for weight-loss and weight-maintenance arms ($n = 6$ studies) (Supplemental Figures 3 and 4). A quality assessment that was performed with the use of grading of recommendations assessment, development, and evaluation criteria downgraded the evidence from RCTs to a moderate quality because of a potential selection bias that was due to lack of allocation concealment, and the evidence from non-RCTs was rated as being of very-low quality (29) (Supplemental Table 2).

Effect of weight loss on serum 25(OH)D

In a meta-analysis, the WMD in the change in serum 25(OH)D between subjects who were randomly assigned to weight loss and subjects who were randomly assigned to weight maintenance was 3.11 nmol/L (95% CI: 1.38, 4.84 nmol/L) and was significant ($P < 0.001$) (Figure 2). In a meta-analysis of nonrandomized trials, serum 25(OH)D significantly increased by 4.85 nmol/L (95% CI: 2.59, 7.12 nmol/L; $P < 0.001$) in subjects in weight-loss groups compared with subjects in weight-maintenance groups. Overall, in both randomized and nonrandomized trials, the relative increase in serum 25(OH)D in the weight-loss group was also significant (3.76 nmol/L; 95% CI: 2.38, 5.13 nmol/L; $P < 0.001$). No heterogeneity was detected in randomized, nonrandomized, and overall meta-analyses ($I^2 = 0\%$, $P = 0.472$). There was no evidence of publication bias (Supplemental Figure 5) or small study effects ($P$-Egger’s test = 0.561).
In sensitivity analyses, the exclusion of the 3 trials that were subject to a known or unknown seasonal influence did not alter pooled results in a meaningful way. The withholding of a single trial for which supplemental vitamin D intake was not available did not alter the pooled results appreciably nor did the withholding of each other trial in turn from the analyses. The pooling of studies with supplemental vitamin D intakes $\leq 400$ IU/d from either study- or self-administered dietary supplements resulted in an overall WMD in serum 25(OH)D of 4.41 nmol/L (95% CI: 1.82, 7.00 nmol/L; $P < 0.001$, $n = 9$ studies). The exclusion of the 6 studies in which supplemental vitamin D was administered to participants during the intervention period did not alter the results meaningfully, whereas a nonsignificant WMD in serum 25(OH)D of 3.84 nmol/L (95% CI: $-4.58$, 12.25 nmol/L; $P = 0.37$) was observed in the 4 studies ($n = 178$) that reported no supplemental vitamin D intake. A sensitivity analysis of pooled data from trials with the use of a common 25(OH)D assay methodology [radio-immunoassay (DiaSorin); $n = 10$ studies] remained significant (WMD: 3.10 nmol/L; 95% CI: 0.44, 5.76 nmol/L; $P \leq 0.022$), and the pooling of only those trials with dietary interventions (i.e., no exercise component; $n = 8$ studies) resulted in an overall WMD of 4.39 nmol/L (95% CI: 1.80, 6.97 nmol/L; $P < 0.001$).

In sensitivity analyses with the use of meta-regression to examine the effect of potential confounders on the effect size, percentage of women, mean age, supplemental vitamin D (IU/d), baseline 25(OH)D, baseline BMI, serum 25(OH)D analytic CV, randomized study (yes or no), and time to first follow-up showed no association with the change in serum 25(OH)D (all $P \geq 0.172$).

**Dose-response effect of change in adiposity on serum 25(OH)D**

No dose-response relation was observed between the change in adiposity and the change in serum 25(OH)D. A 1-U decrease in weight (kg; $n = 14$ studies), BMI ($n = 14$ studies), body fat (kg; $n = 10$ studies), and percentage of body fat ($n = 11$ studies) in the intervention group compared with the control group was not related to the WMD in the change in serum 25(OH)D (all $P \geq 0.176$).

**DISCUSSION**

In this systematic review of the effect of weight loss on circulating vitamin D, random assignment to weight loss compared with weight maintenance resulted in a small but significantly
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<td>33.1</td>
<td>62.7</td>
</tr>
<tr>
<td>Overweight and obese adults at risk of T2DM</td>
<td>28</td>
<td>59</td>
<td>52</td>
<td>52</td>
<td>902</td>
<td>33.1</td>
<td>62.7</td>
<td></td>
</tr>
</tbody>
</table>

1T2DM, type 2 diabetes mellitus; 25(OH)D, serum 25-hydroxyvitamin D.

All values are means unless otherwise specified.

Reported values.

Mean ± SD (all such values).

Mean.  

Range.

greater increase in serum 25(OH)D of 3.11 nmol/L. Results were similar for nonrandomized trials and when pooled across randomized and nonrandomized trials. Overall pooled results remained significant in sensitivity analyses except when the analyses were restricted to the limited data from 4 small studies in which no supplemental vitamin D was consumed. No evidence of a dose-response relation between the change in adiposity and the change in serum 25(OH)D was shown overall.

Although our study benefited from the use of 2 types of pooled analyses, we failed to detect a dose-response effect with the use of meta-regression. In contrast, in a recent systematic review with meta-regression of uncontrolled before-after data from weight-loss studies, relations between the change in serum 25(OH)D and the change in weight and the percentage of body fat approaching statistical significance were observed (42). The lack of the dose-response effect noted in our study may have been due to little between-study variation in the change in adiposity or serum 25(OH)D or because of the limited statistical power that resulted from the small number of controlled studies available (31).

Because most studies included vitamin D supplementation, it was possible that the relative increase in serum 25(OH)D that was observed after weight loss compared with after weight maintenance was as a result of an improved bioavailability of supplemental vitamin D (12). Nonetheless, our results support the hypothesis that vitamin D that is stored in body fat and skeletal muscle contributes to serum 25(OH)D concentrations during weight loss. We were unable to differentiate between these 2 potential sources of vitamin D in our analyses, and skeletal muscle loss would likely have been attenuated in trials with an exercise component. However, the restriction of the analysis to trials without an exercise component produced a similar overall pooled-effect estimate. Although most 25(OH)D circulates in the blood, adipose tissue is the major site of storage of vitamin D in the body as has been shown in animals and in human tissue samples collected as biopsies, as amputation specimens, and at autopsy (43, 44). In rats, orally administered vitamin D has been shown to rapidly accumulate in adipose tissue and is subsequently released into the circulation over several months (16, 45). During fasting, the release of the vitamin D from rat adipose tissue was augmented, which led to increased serum 25(OH)D after its hepatic hydroxylation (16). Whether this process occurs in human weight loss is unknown, and although our study supports this hypothesis, we were limited in that we only examined the gross relation between weight loss and the change in serum 25(OH)D, which may have been subject to aggregation bias (31).

In the nonrandomized trials included in the meta-analysis, weight-maintenance participants were either recruited for weight maintenance per se or had failed to lose weight while enrolled in a weight-loss study. Therefore, the subjects likely differed from participants in the weight-loss group in other behaviors such as adherence to study vitamin D–supplementation protocols. This difference might have partially accounted for the larger effect size observed in the pooled analysis of nonrandomized trials. Because the pooled analysis of randomized trials likely produced an estimate that was closer to the true effect size (46, 47), we note that the increase in serum 25(OH)D after weight loss was small. This finding was not unexpected because, although concentrations of vitamin D in adipose tissue ranged from 1280 to 8360 IU/kg in unsupplemented and supplemented individuals,
respectively (44), the weight loss observed in the current study may have had a limited capacity to raise circulating vitamin D concentrations substantially because of the long time period over which fat tissue was catabolized and the 2-wk half-life of serum 25(OH)D (23). However, although not unexpected, the small effect size should be interpreted with caution because the reported CVs in many of the studies were of a similar magnitude.

Despite the consistent negative association between BMI and serum 25(OH)D observed in cross-sectional surveys (48), the absolute difference in serum 25(OH)D concentrations between normal-weight and overweight individuals may be as little as 2 nmol/L and is somewhat larger between normal weight and obese individuals (49, 50). The presence of this well-established association between BMI and serum 25(OH)D in the absence of changes in adiposity was not well explained by our study. However, background lipid turnover occurs continuously, and this turnover has been shown to occur at a significantly reduced rate in the context of obesity with the mean age of lipids being 2y compared with 1.6 y in nonobese individuals (51). The lower rate of triglyceride turnover may inhibit the release of vitamin D from adipose tissue, thereby contributing to the lower circulating concentrations of 25(OH)D that have been observed in obesity. Alternatively, another hypothesis that may explain the lower circulating concentrations of 25(OH)D in overweight and obesity is related to the volume of distribution of vitamin D, which is believed to be greater in overweight individuals because of the expanded mass of adipose tissue (11). According to this model, vitamin D is distributed across the body’s tissue compartments in the same way as in nonoverweight individuals (i.e., with most vitamin D deposited in fat tissue), but because of the greater proportion of adipose tissue, less vitamin D is available for circulation and subsequent hydroxylation. Although we showed no evidence for a dose-response relation between a reduction in the percentage of body fat and an increase in serum 25(OH)D in the current study, we could not rule out that the change in volume of distribution was responsible for or augmented the increase in serum 25(OH)D that was observed after weight loss.

In conclusion, the results of our study extend the findings of other meta-analyses and trials that have shown no evidence of an effect of supplemental vitamin D on the reduction of obesity or its related diseases (3–7, 52–55). Although these previous studies have refuted the causal link between elevated serum 25(OH)D concentrations and weight reduction, we have taken a further step and provided some evidence in support of reversed causation, showing that weight reduction leads to an increase in serum 25(OH)D concentrations under similar conditions of supplemental vitamin D intake. In light of the current evidence, perhaps the

![FIGURE 2](image-url)
most important clinical and public health implication is that, rather than striving to optimize overweight patients’ vitamin D concentrations with the aim of weight reduction, the focus should remain on interventions that are known to induce favorable changes in weight such as a lifestyle change and environmental modification (56, 57). As an additional benefit, people who lose weight are likely to improve their vitamin D concentrations, albeit by a small amount. Although the current study provides some evidence of an increase in circulating 25(OH)D in response to weight loss, additional adequately powered RCTs that are designed to avoid confounding by vitamin D-supplement use, the method of serum 25(OH)D analysis, seasonality, and sun exposure are required to confirm the findings reported here. In addition, fundamental studies are needed to investigate the mechanisms that underlie the observed increase in serum 25(OH)D after weight loss.

We thank Peter Herbison, Department of Preventive and Social Medicine, University of Otago, for his statistical advice.

The authors’ responsibilities were as follows—SRM: designed and conducted the research, performed the statistical analyses, wrote the manuscript, and had primary responsibility for the final content of the manuscript; ASH: conducted the research; and all authors: contributed to the review of the manuscript and read and approved the final draft of the manuscript. None of the authors reported a conflict of interest related to the study.

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11. Drincic AT, Armas LA, Van Diest EE, Heaney RP. Volumetric dilution, rather than sequestration best explains the low limit to optimize vitamin D concentrations with the aim of weight reduction, the focus should remain on interventions that are known to induce favorable changes in weight such as a lifestyle change and environmental modification (56, 57). As an additional benefit, people who lose weight are likely to improve their vitamin D concentrations, albeit by a small amount. Although the current study provides some evidence of an increase in circulating 25(OH)D in response to weight loss, additional adequately powered RCTs that are designed to avoid confounding by vitamin D-supplement use, the method of serum 25(OH)D analysis, seasonality, and sun exposure are required to confirm the findings reported here. In addition, fundamental studies are needed to investigate the mechanisms that underlie the observed increase in serum 25(OH)D after weight loss.

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