Vitamin D oral intermittent treatment (DO IT) study, a randomized clinical trial with individual loading regimen

Jean-Pierre Rothen1,*, Jonas Rutishauser2, Philipp N. Walter1, Kurt E. Hersberger1 & Isabelle Arnet1

Comparison of several regimens of oral vitamin D including an individually calculated loading regimen with the aim of achieving serum values > 75 nmol/l. Interventional, randomized, 3-arm study in vitamin D-deficient outpatients. Participants were allocated to supplementation of 24,000 IU vitamin D monthly over three months, using either a monthly drinking solution (Vi-De 3) or capsule (D3 VitaCaps), or an individualized loading regimen with the capsules taken weekly. For the loading regimen, the cumulative dose was calculated according to baseline 25-hydroxy-vitamin D (25(OH)D) serum value and body weight. Main inclusion criteria were age ≥ 18 years and 25(OH)D serum concentration < 50 nmol/l. The primary outcome was 25(OH)D serum concentration one week after treatment termination. Secondary endpoints were patient’s preferences and adverse events. Full datasets were obtained from 52 patients. Mean 25(OH)D values were statistically significant higher after a loading regimen compared to a monthly administration of 24,000 IU vitamin D (76.4 ± 15.8 vs 61.4 ± 10.8 nmol/l; p < 0.01). All patients treated with the loading regimen reached sufficient 25(OH)D values > 50 nmol/l. Serum 25(OH)D values > 75 nmol/l were observed more frequently in patients taking the loading regimen (47% vs 11% drinking solution vs 12% capsules). Vitamin D-related adverse effects did not occur in any treatment groups. Capsules were preferred by 88.5% of the patients. Compared to treatments with monthly intake of 24,000 IU vitamin D, the intake of an individually calculated weekly loading regimen was able to raise serum concentrations > 50 nmol/l in all cases within a safe range.

Abbreviations

25(OH)D 25-Hydroxy-vitamin D
FCN Swiss federal commission of nutrition
IoM Institute of medicine, now national academy of medicine

Vitamin D (cholecalciferol) insufficiency corresponding to serum 25-hydroxy-vitamin D (25(OH)D) concentrations < 50 nmol/l occurs frequently, especially during the winter period1,2 and in elderly people who can only synthesize reduced amounts of vitamin D in their skin3. Other risk factors include reduced UV-B effectiveness in dark skin, overweight, lack of exercise, and underexposure to sunlight due to cultural or religious dress codes4-7. The serum concentration is considered the most significant indicator for vitamin D storage, with 25(OH)D values < 25 nmol/l indicating a deficiency, 25–50 nmol/l insufficiency, and values > 50 nmol/l sufficiency8. Optimal values are > 75 nmol/l9-11, without exact definitions of the upper reference value12.

Vitamin D can be supplemented at every age for therapeutic or prophylactic purposes. However, dosage recommendations differ. The US Institute of Medicine (IoM) recommends a daily intake of 600 IU vitamin D for adults aged 19–59 years, 800 IU for those aged > 60 years and 1,500–2,000 IU for those with severe deficiency13. The maximum tolerable amount according to the IoM, the European Food Safety Authority and the Swiss Federal Commission of Nutrition (FCN) is 4,000 IU vitamin D per day11-13. The upper limit for adults according to the Endocrine Society Clinical Practice Guideline is 10,000 IU vitamin D per day12.

1Pharmaceutical Care Research Group, Department of Pharmaceutical Sciences, University of Basel, Petersplatz 14, Postfach 2148, 4001 Basel, Switzerland. 2Clinical Trial Unit, University Hospital of Basel, Kantonsspital Baden, Basel, Switzerland. 3Institute of Laboratory Medicine, Solothurner Spitäler, Switzerland. 4*email: jp.rothen@unibas.ch
Due to its half-life of about 2 months\textsuperscript{16}, the intermittent weekly or monthly intake of cumulative doses of cholecalciferol achieves identical 25(OH)D serum values compared to corresponding daily dosage\textsuperscript{17–19} at steady state. A loading dose regimen based on body weight and baseline 25(OH)D values has recently been suggested to initiate substitution and obtain rapid correction of vitamin D deficiency\textsuperscript{9}. A formula for a loading regimen has been proposed with doses following the recommendations of the IoM and the FCN\textsuperscript{20}. Its practicality has been confirmed at doses exceeding the recommendations\textsuperscript{21}.

In earlier trials comparing weekly to monthly cumulative administration of 800 IU vitamin D in liquid or solid formulation, an optimal 25(OH)D value of > 75 nmol/l was achieved only by a minority of patients after 3 or 6 months of treatment using either regimen\textsuperscript{22,23}.

The aims of this study were a) to investigate whether a loading regimen without exceeding the maximum dosage of 4,000 IU vitamin D per day as recommended by the IoM\textsuperscript{13} and the FCN\textsuperscript{15} would lead to mean 25(OH)D levels that are higher than after a monthly administration; the monthly substitution of 24,000 IU vitamin D either as capsules or as alcoholic drinking solution will lead to 25(OH)D-values in the same range.

**Methods**

**Study hypothesis.** A weekly loading regimen with capsules containing 24,000 IU vitamin D during an individually calculated duration will be able to raise mean 25(OH)D levels higher than a monthly administration; the monthly substitution of 24,000 IU vitamin D either as capsules or as alcoholic drinking solution will lead to 25(OH)D-values in the same range.

**Setting.** This was an interventional, randomized, 3-arm study using two formulations of vitamin D. The liquid formulation was Vi-De 3 monthly dose bottle (Wild & Co. Inc., 4132 Muttenz, Switzerland; 24,000 IU/5 ml in 65% alcoholic solution). The solid formulation was newly developed gelatin-free soft capsules (24,000 IU/capsule; D\textsuperscript{3} VitaCaps). Patients were administered 24,000 IU vitamin D monthly as drinking solution (group drinking solution) or as monthly capsules (group capsules), or as a loading regimen (group loading regimen) (Fig. 1). The loading regimen consisted of the weekly intake of one 24,000 IU vitamin D capsule without initial bolus. The number of weeks was calculated as follows: 40*(100–25(OH)D baseline concentration [nmol/l])*body weight [kg]/24,000 using the formula adapted from\textsuperscript{20}. Numbers were rounded to the next entire number of capsules.
adherence as % predicted (number of doses taken / number of doses prescribed) * 100) 24. Sample size was bottles or empty blister cavities were defined as adherence. Time4Med smart card data were used to calculate adherence range 40–150 U/l), and creatinine were measured at screening and one week after termination the study (reference range 2.10–2.55 mmol/l), phosphate (reference range 0.74–1.52 mmol/l), alkaline phosphatase (reference range 50–250 nmol/l), intact parathyroid hormone (reference range 1.59–12.0 pmol/l), total calcium (reference range 2.25–2.65 mmol/l), and 25(OH)D serum values between the patient groups were compared using the Wilcoxon test. p-values < 0.05 were considered significant. To compare numerical variables between the groups. Mean 25(OH)D-values at screening and at the final visit were calculated according to the assumed difference in the mean 25(OH)D serum values between the patient groups was calculated according to the assumed difference in the mean 25(OH)D serum values between the patient groups with monthly intake of 24,000 IU cholecalciferol and the patient group with loading regimen. We assumed that 25(OH)D serum value reach 55 ± 18 nmol/l following a monthly treatment22, and 75 nmol/l following the loading regimen, which corresponds to a difference of 20 nmol/l. Thus, we need 37 patients (17 patients per group + 3 drop-outs) to detect whether the stated difference exists between the two means with a power of 90%, a significance level at 5%, and a drop-out rate of 10%25. The statistical evaluation was carried out using SPSS (IBM, version 27). Values are presented as mean ± standard deviations (s), median with quartiles and as percentages, where appropriate. Mann–Whitney U-test was used to compare numerical variables between the groups. Mean 25(OH)D-values at screening and at the final visit were compared using the Wilcoxon test. p-values < 0.05 were considered significant.

### Randomization.
Patients were randomly allocated to one of the three treatment groups using 1:1:1 block randomization with block size 6 or 9. Identical plain envelopes containing 2 to 3 case report forms per group were placed manually in random order in plastic boxes. Physicians took one case report forms per patient from a plastic box. Both patients and recruiting physicians were aware of treatment allocation. Patients were asked to return packings at the final study visit.

### Statistical analysis.
Visual examination of the returned medication packings was performed. Empty bottles or empty blister cavities were defined as adherence. Time4Med smart card data were used to calculate adherence as % predicted ([number of doses taken / number of doses prescribed] * 100)24. Sample size was calculated according to the assumed difference in the mean 25(OH)D serum values between the patient groups with monthly intake of 24,000 IU cholecalciferol and the patient group with loading regimen. We assumed that 25(OH)D serum value reach 55 ± 18 nmol/l following a monthly treatment22, and 75 nmol/l following the loading regimen, which corresponds to a difference of 20 nmol/l. Thus, we need 37 patients (17 patients per group + 3 drop-outs) to detect whether the stated difference exists between the two means with a power of 90%, a significance level at 5%, and a drop-out rate of 10%25.

### Patients and outcome measures.
Six general practitioners in and near Basel (Switzerland) who were experienced in performing research studies participated in this study. Patients were enrolled in an outpatient setting during routine medical visits. Inclusion criteria were age ≥ 18 years and vitamin D insufficiency (serum 25(OH)D concentration < 50 nmol/l). Exclusion criteria were hypercalcaemia and nephrolithiasis. The primary outcome measure was 25(OH)D serum concentration. Secondary outcomes were patients’ preferences, adherence and adverse events.

### Randomization.
Patients were randomly allocated to one of the three treatment groups using 1:1:1 block randomization with block size 6 or 9. Identical plain envelopes containing 2 to 3 case report forms per group were placed manually in random order in plastic boxes. Physicians took one case report forms per patient from a plastic box. Both patients and recruiting physicians were aware of treatment allocation. Patients were asked to return packings at the final study visit.

### Study visits, laboratory measurements and questionnaires.
Serum concentrations of 25(OH)D (reference range 50–250 nmol/l), intact parathyroid hormone (reference range 1.59–12.0 pmol/l), total calcium (reference range 2.10–2.55 mmol/l), phosphate (reference range 0.74–1.52 mmol/l), alkaline phosphatase (reference range 40–150 U/l), and creatinine were measured at screening and one week after termination the study medication, The Institute of Laboratory Medicine of the Solothurn Hospitals performed the analysis using the Architect analysis system by Abbott AG, CH-6341 Baar.

The physicians asked the patient’s preferred date of intake and wrote it directly on the packings (for example: 10 Oct/10 Nov/10 Dec). Patients were provided with the Time4Med smart card24, a device for the electronic assessment of adherence which registered date and time of study medication intake upon patient activation.

Patients were not to travel south of 35° latitude during the trial. Study visits were medication dispense and the final visit. During the latter, five questions with dichotomous answer options were asked addressing the following items: 1) Did you stay during the treatment south of latitude 35? [Yes, No]. 2) Have you noticed any listed unexpected events? [Yes (please specify), No]. 3) Have you noticed any other unexpected events? [Yes (please specify), No]. 4) How did you manage to take your medication in the past 3 months? [well, poorly]. 5) Do you prefer the intake of 24,000 IU vitamin D as drinking solution or as capsules?

### Statistical analysis.
Visual examination of the returned medication packings was performed. Empty bottles or empty blister cavities were defined as adherence. Time4Med smart card data were used to calculate adherence as % predicted ([number of doses taken / number of doses prescribed] * 100)24. Sample size was calculated according to the assumed difference in the mean 25(OH)D serum values between the patient groups with monthly intake of 24,000 IU cholecalciferol and the patient group with loading regimen. We assumed that 25(OH)D serum value reach 55 ± 18 nmol/l following a monthly treatment22, and 75 nmol/l following the loading regimen, which corresponds to a difference of 20 nmol/l. Thus, we need 37 patients (17 patients per group + 3 drop-outs) to detect whether the stated difference exists between the two means with a power of 90%, a significance level at 5%, and a drop-out rate of 10%25.

The statistical evaluation was carried out using SPSS (IBM, version 27). Values are presented as mean ± standard deviations (s), median with quartiles and as percentages, where appropriate. Mann–Whitney U-test was used to compare numerical variables between the groups. Mean 25(OH)D-values at screening and at the final visit were compared using the Wilcoxon test. p-values < 0.05 were considered significant.

### Table 1. Patient's characteristics included to the study (n = 58).

| Measure                  | All (n = 58) | Drinking solution (n = 20) | Capsules (n = 19) | Loading regimen (n = 19) |
|-------------------------|-------------|---------------------------|------------------|-------------------------|
| Age [years] m ± s (range)| 49 ± 17.6   | 47 ± 19.6                 | 51 ± 18.1        | 48 ± 15.4               |
|                         | (19–89)     | (19–89)                   | (23–82)          | (19–82)                 |
| Male [n]                | 25          | 8                         | 7                | 10                       |
| Female [n]              | 33          | 12                        | 12               | 9                        |
| Height [m] m ± s (range)| 1.72 ± 0.09 | 1.72 ± 0.11               | 1.70 ± 0.08      | 1.72 ± 0.09              |
|                         | (1.50–1.89) | (1.50–1.89)               | (1.53–1.84)      | (1.59–1.88)              |
| Weight [kg] m ± s (range)| 80.3 ± 18.0| 78.5 ± 17.7               | 75.7 ± 12.0      | 84.9 ± 22.2              |
|                         | (43–124)    | (43–124)                  | (54–99)          | (53–120)                 |
| BMI [kg/m²] m ± s (range)| 27.2 ± 5.4 | 26.4 ± 5.4               | 26.2 ± 3.3       | 28.1 ± 6.7               |
|                         | (19.1–41.0)| (19.1–41.0)              | (22.0–32.6)      | (19.4–40.1)              |
| Comedication [n] m ± s (range)| 1.6 ± 1.7 | 1.5 ± 1.9                | 1.8 ± 1.7        | 1.5 ± 1.6                |
|                         | (0–6)       | (0–6)                     | (0–6)            | (0–6)                    |

All (n = 58) Drinking solution (n = 20) Capsules (n = 19) Loading regimen (n = 19)

Table 1. Patient's characteristics included to the study (n = 58).
Results. A total of 58 patients were recruited between 18th October 2019 and 6th March 2020 and equally distributed across the three groups (drinking solution: 20; capsules: 19; loading regimen: 19). Table 1 shows the baseline characteristics of the participants. The three groups did not differ in mean ± SD age (49 ± 17.6 years), weight (80.3 ± 18.0 kg), gender distribution (57% women) or number of comediations (1.6 ± 1.7). Six subjects were excluded (2 from each group) because they missed the final visit or refused a second blood sample (five patients), or spent holidays south of latitude 35° during the study period (one patient). The study analysis was performed with data from 52 patients (drinking solution: 18; capsules: 17, loading regimen: 17). The cumulative dose of vitamin D throughout the study was 72,000 IU for the groups with monthly intake, and 240,000 (range 144,000–312,000) IU for the loading regimen. The duration of the loading regimen was slightly shorter than 3 months with a mean of 9.9 (range: 6–13) weeks.

25(OH)‑vitamin D serum concentrations. 25(OH)D values increased from a mean of 32.9 ± 9.2 nmol/l at screening to a mean of 66.4 ± 14.8 nmol/l (Table 2) at final visit. Values after the loading regimen raised to mean 76.4 ± 15.8 nmol/l and were statistically significantly higher than after a monthly drinking solution (65.2 ± 10.2 nmol/l; p = 0.01) and after monthly capsules (57.4 ± 11.4 nmol/l; p < 0.01). There was no statistically significant difference between the mean 25(OH)D values after either monthly treatment (Table 2). Sufficient 25(OH)D values (> 50 nmol/l) were reached in 94% (17/18) of the patients taking the drinking solution and in 65% (11/17) of those taking the capsules (difference not significant; Table 2). In both groups, two patients achieved optimal 25(OH)D values (> 75 nmol/l). In the loading regimen group, all patients (17/17) achieved sufficient 25(OH)D values (> 50 nmol/l) and 47% (8/17) of them reached optimal values (> 75 nmol/l). The highest value of 114 nmol/l 25(OH)D was observed after a loading regimen over eleven weeks (Fig. 2).

Other biomarkers. All biomarkers’ values remained unchanged or changed in the expected direction between screening and final visit. Mean serum parathyroid hormone levels decreased non-significantly from 7.06 to 6.26 pmol/l at the final visit, mean serum calcium levels remained unchanged (2.39 vs 2.40 mmol/l), mean serum phosphate concentrations increased from 1.28 to 1.39 mmol/l (p = 0.02), mean serum alkaline phosphatase decreased from 69.2 to 66.1 U/l (p = 0.04).

Unexpected events. Among the 58 patients who were enrolled in the study, six (10.3%) reported an unexpected event (Table 3). None of the reported events was considered related to cholecalciferol administration. The only serious event was an episode of pancreatitis, which according to Swissmedic, the competent health authority, was likely related to another medication.

Patient preferences. A total of 46 (88.5%) patients managed the intake well. From the six patients who reported problems with their study medication, five (9.6%) complained about the bad and/or alcoholic taste of the drinking solution and one (1.9%) about difficulties to remember the weekly intake of the loading regimen. When choosing freely, 46 patients (88.5%) would opt for capsules, five (9.6%) for the alcoholic drinking solution. One (1.9%) patient was indifferent.

Adherence. From the totally delivered and scheduled 274 doses, a total of 273 (99.6%) were assessed visually, 261 (95.3%) were recorded electronically. Taking adherence reached 100% with the monthly drinking solution, 81% with the monthly capsules and 99% with the weekly loading regimen. Four patients taking monthly...
capsules registered only one intake electronically instead of three, their taking adherence according visual assessment was 100%.

Discussion

The administration of an individually calculated loading regimen of weekly 24,000 IU vitamin D enabled to reach significantly higher 25(OH)D values compared to the monthly administration of a cumulative daily dose of 800 IU vitamin D. All patients in this latter group had sufficient, and half of them optimal 25(OH)D levels. There was no statistical difference in the increase of vitamin D levels after supplementation of 24,000 IU monthly between patients taking the drinking solution and those on oily soft-capsules. Our results thus show no difference between the newly developed capsules and the drinking solution. In both groups, a majority of the patients achieved sufficient 25(OH)D values, and only 12% reached the optimal range. This result is in line with previous studies and indicates that the capsules are suitable for use in general medical practice. Additionally, patients’ preferences were unequivocally in favour of capsules.

The toxic range was not reached by far. This demonstrates that the loading dose regimen more frequently leads to optimal 25(OH)D serum values (> 75 nmol/l) without exceeding the maximum dosage of 4,000 IU vitamin D per day.

To calculate the loading regimen, we adapted a published formula. Our equation subtracts the baseline 25(OH)D value from 100 nmol/l, whereas the original formula uses 75 nmol/l. The increase is justified by the fact that in the original publication, only 76% of the patients achieved a serum 25(OH)D level > 50 nmol/l, and 48% of them achieved a serum 25(OH)D level > 75 nmol/l. Especially, in the group obtaining a cumulative dose

Figure 2. Representation of median 25(OH)D values at screening (white boxes) and one week after treatment termination (grey boxes) per treatment groups (Drinking solution, Capsules, and Loading regimen) as Whisker boxplot. Significant differences are marked with *.

Table 3. Reported unexpected events at final visit.

| Participant code | Treatment group | Unexpected event                                      | Severity/Seriousness |
|------------------|-----------------|------------------------------------------------------|----------------------|
| KD16             | Drinking solution | Facial acne                                         | Mild, non-serious    |
| SE56             | Capsules         | Recurrent light neck scratching and headaches for 4 weeks | Mild, non-serious    |
| PP72             | Capsules         | Diarrhoea once                                     | Mild, non-serious    |
| MR02             | Loading regimen  | Flu-like infection, 3 days of cough and fever       | Mild, non-serious    |
| MR59             | Loading regimen  | Occasional dizziness after taking study medication   | Mild, non-serious    |
| KD04             | Loading regimen  | Pancreatitis                                        | Severe, serious      |
of 200'000 IU vitamin D which is the closest to our regimen, the mean 25(OH)D increased to 87.7 ± 26.9 nmol/l. This overall result leaves room for improvement. Thus, in analogy to a dose-finding study, we selected 100 nmol/l as the next higher target value in the formula to be susceptible to increase the serum 25(OH)D values consistently to sufficient levels. With our adjustment, we obtained 100% of the serum 25(OH)D values > 50 nmol/l and 47% of them > 75 nmol/l, which matches our expected target values.

Our loading regimen includes no loading dose, but 24,000 IU single doses. This corresponds approximately to the upper level of vitamin D that is physiologically produced in the skin. Especially, no adverse events were probably not related to the administration of the study medication. Further, no pathologic laboratory values were observed that could be attributed to the administration of vitamin D. Especially, no patient developed hypercalcaemia. Overdose has not been observed even when using the loading regimen.

The taking adherence was high compared to other adherence trials performed in the similar setting of supplementation. This might be attributed to highly motivated study participants who were recruited by their general practitioner or to a large acceptance of vitamin D supplementation in the general population. In addition, noting the exact days for the medication intake on the packings may have acted like a reminder and facilitated a regular intake and thus, a high adherence. Compared to affixing a label with a dosing instruction (such as “Take a capsule once monthly”), the instruction was an individualized consensus (such as “3 OCT / 3 NOV / 3 DEC”) with the patient, resembling to shared decision-making.

The number of six withdrawals (10.3%) seems high. However, five patients missed their final visit, which is probably linked to the lockdown installed during the COVID pandemic.

Our study has several strengths. First, the upper dose limit as defined by the FCN dosage recommendations was respected, also in the loading regimen group. Second, we included only patients with a confirmed vitamin D insufficiency with 25(OH)D values < 50 nmol/l. Third, preliminary calculation with the loading regimen formula enabled us to anticipate the study duration at approximately 3 months. Thus, a similar study duration was obtained for each group, rendering our results more robust. Finally, our results can be generalized, because the six general practitioners are very diverse and represent the usual internal medical situations.

We acknowledge some limitations. First, the study lasted 3 months for the monthly regimens and up to 13 weeks with the loading regimen, and not the whole winter half-year. This allowed us to extend the recruitment period. Second, the number of study patients is small. Nevertheless, our findings correspond to those of other studies.

To conclude, a supplementation regimen with capsules containing 24,000 IU vitamin D over an individually calculated duration leads to sufficient values (> 50 nmol/l) in all patients and to optimal values (> 75 nmol/l) in approximately 50% of the patients. Prescribers should take into account patient’s preference to support a shared decision-making process when prescribing a medication such as vitamin D that exists in different medication formulation.

Received: 13 April 2021; Accepted: 24 August 2021
Published online: 21 September 2021

References
1. Adams, J. S. & Hewison, M. Update in vitamin D. J. Clin. Endocrinol. Metab. 95, 471–478 (2010).
2. Quarenghi, M. C. et al. Vitamin D deficiency in the sunny corner of Switzerland. Praxis 106, 1323–1330 (2017).
3. Hintzpeter, B., Mensink, G. B., Thierfelder, W., Muller, M. J. & Scheidt-Nave, C. Vitamin D status and health correlates among German adults. Eur. J. Clin. Nutr. 62, 1079–1089 (2008).
4. Kaddam, I. M. et al. Prevalence of vitamin D deficiency and its associated factors in three regions of Saudi Arabia. Saudi Med. J. 38, 381–390 (2017).
5. Abboud, M., Rybcyn, M. S., Rizk, R., Fraser, D. R. & Mason, R. S. Sunlight exposure is just one of the factors which influence vitamin D status. Photochem. Photobiol. Sci. 16, 302–313 (2017).
6. Zittermann, A., Ernst, J. B., Gummett, J. F. & Borgermann, J. Vitamin D supplementation, body weight and human serum 25-hydroxyvitamin D response: A systematic review. Eur. J. Nutr. 53, 367–374 (2014).
7. Hardi, J., Reinhard, S., Conzelmann, M., Kressig, R. W. & Brudenaugh, S. A. Vitamin D level in employees of a Swiss University geriatric hospital. Praxis 107, 633–640 (2018).
8. Braegger, C. et al. Vitamin D in the healthy European paediatric population. J. Pediatr. Gastroenterol. Nutr. 56, 692–701 (2013).
9. Dalle Carbonare, L., Valenti, M. T., Del Forno, F., Caneva, E. & Pietrobelli, A. Sunlight exposure is just one of the factors which influence vitamin D status. Photochem. Photobiol. Sci. 16, 302–313 (2017).
10. Zittermann, A., Ernst, J. B., Gummett, J. F. & Borgermann, J. Vitamin D supplementation, body weight and human serum 25-hydroxyvitamin D response: A systematic review. Eur. J. Nutr. 53, 367–374 (2014).
11. Amrein, K. et al. Vitamin D deficiency 2.0: an update on the current status worldwide. Eur. J. Clin. Nutr. 2, 2 (2020).
12. Holick, M. F. et al. Evaluation, treatment, and prevention of vitamin D deficiency: An endocrine society clinical practice guideline. J. Clin. Endocrinol. Metab. 96, 1911–1930 (2011).
13. Ross, A. C. et al. The 2011 report on dietary reference intakes for calcium and vitamin D from the Institute of Medicine: What clinicians need to know. J. Clin. Endocrinol. Metab. 96, 53–58 (2011).
14. EFSA. Scientific opinion on the tolerable upper intake level of vitamin D. EFSA J. 10, 2 (2012).
15. Bischoff-Ferrari, H. A. Empfehlungen der Eidgenössischen Ernährungskommission zur Vitamin-D-Zufuhr für die Schweizer Bevölkerung. in Swiss Medical Forum, Vol. 12 775–778 (EMH Media, 2012).
16. Vieth, R. The pharmacology of vitamin D, including fortification strategies. Vitamin D 2, 995–1015 (2005).
17. Noe, S. et al. Cholecalciferol 20 000 IU once weekly in HIV-positive patients with low vitamin D levels: Result from a cohort study. J. Int. Assoc. Provid. AIDS Care 16, 315–320 (2017).
18. Ish-Shalom, S. et al. Comparison of daily, weekly, and monthly vitamin D3 in ethanol dosing protocols for two months in elderly hip fracture patients. J. Clin. Endocrinol. Metab. 93, 3430–3435 (2008).
19. Takacs, I. et al. Randomized clinical trial to comparing efficacy of daily, weekly and monthly administration of vitamin D3. Endocrine 55, 60–65 (2017).
20. van Groningen, L. et al. Cholecalciferol loading dose guideline for vitamin D-deficient adults. Eur. J. Endocrinol. 162, 805–811 (2010).
21. Wijnen, H., Salemink, D., Roovers, L., Taekema, D. & de Boer, H. Vitamin D supplementation in nursing home patients: Randomized controlled trial of standard daily dose versus individualized loading dose regimen. Drugs Aging 32, 371–378 (2015).
22. Rothen, J. P., Rutishauser, J., Walter, P. N., Hersberger, K. E. & Arnet, I. Oral intermittent vitamin D substitution: Influence of pharmaceutical form and dosage frequency on medication adherence: A randomized clinical trial. BMC Pharmacol. Toxicol. 21, 51 (2020).
23. Cavalier, E., Fache, W. & Souberbielle, J. C. A randomised, double-blinded, placebo-controlled, parallel study of vitamin D3 supplementation with different schemes based on multiples of 25,000 IU doses. Int. J. Endocrinol. 2013, 327265 (2013).
24. Arnet, I., Rothen, J. P., Albert, V. & Hersberger, K. E. Validation of a novel electronic device for medication adherence monitoring of ambulatory patients. Pharmacy 7, 2 (2019).
25. Sample size calculator. (ClinCalc.com).
26. Aspray, T. J. et al. Randomized controlled trial of vitamin D supplementation in older people to optimize bone health. Am. J. Clin. Nutr. 109, 207–217 (2019).
27. Wacker, M. & Holick, M. F. Sunlight and Vitamin D: A global perspective for health. Dermato-Endocrinol. 5, 51–108 (2013).
28. Griffin, G. et al. Perspective: Vitamin D supplementation prevents rickets and acute respiratory infections when given as daily maintenance but not as intermittent bolus: implications for COVID-19. Clin. Med. 2, 2 (2021).
29. Brorsen, A. L., Nordin, K. & Ekblom, K. Adherence to vitamin supplementation recommendations in youth who have undergone bariatric surgery as teenagers: a mixed methods study. Obes. Surg. 2, 2 (2020).
30. Schoenthaler, A., Rosenthal, D. M., Butler, M. & Jacobowitz, L. Medication adherence improvement similar for shared decision-making preference or longer patient-provider relationship. J. Am. Board Fam. Med. 31, 752–760 (2018).

Acknowledgements
We thank the investigators Dr. med. Karen Delport, PD Dr. med. Stefan Erb, Dr. med. Gilliane Petitjean Schelker, Dr. med. Anja Sabine Plack, and Dr. med. Madeleine Rothen who, beyond their daily task as general practitioners, are also dedicated to research. The study medication was provided free of charge by Nutrimed. Laboratory analyses were kindly provided by the Institute of Laboratory Medicine, Solothurn Hospitals in Olten, Switzerland. Funding of publication by the “Publication Fund of University of Basel for Open Access”.

Author contributions
J.P.R. and I.A. developed the study design, collected and analyzed the data and drafted the first version of the manuscript. J.R. participated as clinical advisor of the study and included patients; P.W. participated in investigation and methodology; K.H. participated in funding and supervised the trial. All authors edited and approved the final manuscript.

Competing interests
Jean-Pierre Rothen is an employee of Nutrimed Ltd. All other authors declare that they have no competing interests.

Additional information

Correspondence and requests for materials should be addressed to J.-P.R.

Reprints and permissions information is available at www.nature.com/reprints.

Publisher’s note Springer Nature remains neutral with regard to jurisdictional claims in published maps and institutional affiliations.

Open Access This article is licensed under a Creative Commons Attribution 4.0 International License, which permits use, sharing, adaptation, distribution and reproduction in any medium or format, as long as you give appropriate credit to the original author(s) and the source, provide a link to the Creative Commons licence, and indicate if changes were made. The images or other third party material in this article are included in the article’s Creative Commons licence, unless indicated otherwise in a credit line to the material. If material is not included in the article’s Creative Commons licence and your intended use is not permitted by statutory regulation or exceeds the permitted use, you will need to obtain permission directly from the copyright holder. To view a copy of this licence, visit http://creativecommons.org/licenses/by/4.0/.

© The Author(s) 2021