

High-dose vitamin D₃ in the treatment of severe acute malnutrition: a multicenter double-blind randomized controlled trial

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ABSTRACT

Background: Vitamin D deficiency is common in children with severe acute malnutrition, in whom it is associated with severe wasting. Ready-to-use therapeutic food (the standard treatment) contains modest amounts of vitamin D that do not reliably correct deficiency.

Objective: The aim of this study was to determine whether high-dose oral vitamin D₃ enhances weight gain and development in children with uncomplicated severe acute malnutrition.

Design: We conducted a randomized placebo-controlled trial of high-dose vitamin D₃ supplementation in children aged 6–58 mo with uncomplicated severe acute malnutrition in Pakistan. Participants were randomly assigned to receive 2 oral doses of 200,000 IU vitamin D₃ or placebo at 2 and 4 wk after starting ready-to-use therapeutic food. The primary outcome was the proportion of participants gaining >15% of baseline weight at 8 wk after starting ready-to-use therapeutic food (the end of the study). Secondary outcomes were mean weight-for-height or -length *z* score and the proportion of participants with delayed development at the end of the study (assessed with the Denver Development Screening Tool II), adjusted for baseline values.

Results: Of the 194 randomly assigned children who started the study, 185 completed the follow-up and were included in the analysis (93 assigned to intervention, 92 to control). High-dose vitamin D₃ did not influence the proportion of children gaining >15% of baseline weight at the end of the study (RR: 1.04; 95% CI: 0.94, 1.15, *P* = 0.47), but it did increase the weight-for-height or -length *z* score (adjusted mean difference: 1.07; 95% CI: 0.49, 1.65, *P* < 0.001) and reduce the proportion of participants with delayed global development [adjusted RR (aRR): 0.49; 95% CI: 0.31, 0.77, *P* = 0.002], delayed gross motor development (aRR: 0.29; 95% CI: 0.13, 0.64, *P* = 0.002), delayed fine motor development (aRR: 0.59; 95% CI: 0.38, 0.91, *P* = 0.018), and delayed language development (aRR: 0.57; 95% CI: 0.34, 0.96, *P* = 0.036).

Conclusions: High-dose vitamin D₃ improved the mean weight-for-height or -length *z* score and developmental indexes in children receiving standard therapy for uncomplicated severe acute malnutrition in Pakistan. This trial was registered at clinicaltrials.gov as NCT03170479. *Am J Clin Nutr* 2018;107:725–733.

Keywords: vitamin D, severe acute malnutrition, weight-for-height, weight-for-length, developmental delay, gross motor development, fine motor development, language development, Pakistan

INTRODUCTION

Nearly 20 million children suffer from severe acute malnutrition worldwide (1), an estimated 1.4 million of whom live in Pakistan (2). Children who survive an acute episode of severe acute malnutrition are at increased risk of experiencing long-term adverse effects on their physical and mental health (3, 4), which may compromise their economic productivity as adults (5).

Ready-to-use therapeutic food—an energy-dense micronutrient-enriched paste—represents the mainstay for community treatment of uncomplicated severe acute malnutrition (i.e., where children are clinically well and alert, with good appetite). The WHO has highlighted the need for research to identify adjunctive therapies that may improve response to ready-to-use therapeutic food, including administration of broad-spectrum antibiotics and high-dose vitamin A (1). However, the potential for adjunctive vitamin D to improve weight

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Abbreviations used: CMAM, community management of acute malnutrition; DDST II, Denver Development Screening Tool II; MUAC, mid-upper arm circumference; 25(OH)D, 25-hydroxyvitamin D.

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gain and developmental outcomes in children with severe acute malnutrition has been overlooked. This is surprising, because rickets and vitamin D deficiency are known to be common in children with severe acute malnutrition (6–9), vitamin D deficiency associates with severe wasting in malnourished children (10), and vitamin D supplementation has been shown to enhance weight gain in low-birthweight infants (11). Vitamin D has also been shown to have favorable effects on skeletal muscle function (12), neurodevelopment (13), and immune function (14, 15): its anti-inflammatory and antimicrobial actions might enhance response to standard therapy for severe acute malnutrition, a condition in which both increased systemic inflammation and infections are associated with adverse outcome (16, 17).

Although ready-to-use therapeutic food contains some vitamin D [600 IU/sachet, with each child receiving 1.5–5.0 sachets/d according to body weight (**Supplemental Table 2**)], intake from this source may not be sufficient to consistently elevate circulating concentrations of 25-hydroxyvitamin D [25(OH)D] into the optimal range in children with severe acute malnutrition, given the high prevalence of vitamin D deficiency in this group (6–9) and the presence of a systemic inflammatory response that may dysregulate vitamin D metabolism and increase vitamin D requirements (18). We hypothesized that the addition of high-dose vitamin D supplementation to ready-to-use therapeutic food would be effective in elevating serum 25(OH)D concentrations into the high physiologic range in children with severe acute malnutrition, and that this would improve weight gain and developmental indexes over the initial 8 wk of treatment. We tested this hypothesis by conducting a randomized placebo-controlled trial.

METHODS

Trial design and setting

We conducted a multicenter 2-arm parallel double-blind randomized placebo-controlled trial with a one-to-one allocation ratio. Participants were recruited from four outpatient therapeutic program centers (Samina, Jhok Utra, Aali Wala, and Kot Chutta) run by the National Program for Family Planning and Primary Health Care in the Dera Ghazi Khan District of Southern Punjab in Pakistan. This socioeconomically disadvantaged area is frequently affected by floods, and there is a high prevalence of illiteracy, overcrowding, and severe acute malnutrition. The area has a low prevalence of malaria.

Approvals, consent processes and registration

The study was approved by the Ethical Review and Advanced Study Research Board of the University of Punjab, Pakistan (reference 9/2352-ACAD), the Integrated Reproductive Maternal & Newborn Child Health & Nutrition Program, Punjab, Pakistan, and the District Health Office of the Dera Ghazi Khan District, Punjab, Pakistan. Parents of all potentially eligible outpatient therapeutic program attendees were provided with information about the study in their native language by a doctor or a health visitor at participating centers, and informed consent, confirmed by signature or thumb impression, was obtained from those who gave permission for their child to take part in the study. This study was registered at clinicaltrials.gov as NCT03170479.

Eligibility criteria

Children aged 6–59 mo at enrollment whose parents gave consent for them to participate were potentially eligible if they had severe acute malnutrition without complications, as defined by WHO [i.e., children with a mid-upper arm circumference (MUAC) of <115 mm, a weight-for-height *z* score <−3, or grade 1–2 bilateral edema who were clinically well and alert with good appetite (1)]. Exclusion criteria were either ingestion of a dose of vitamin D >200,000 IU (5 mg)/mo in the last 3 mo (confirmed by medical records, or by maternal recall where these were unavailable) or the presence of complications of severe malnutrition (severe dehydration, severe anemia, severe pitting edema, anorexia, hypothermia, hyperpyrexia, acute lower respiratory infection, or hypoglycemia).

Baseline assessment

Children aged 6–59 mo whose parents gave consent for them to participate underwent the following baseline assessment. A structured sociodemographic and nutritional questionnaire was administered to capture information on participants' demographic details, parental occupation, education, monthly income, and nutritional intake. Gestational age was taken from the antenatal record where delivery occurred in hospital, or was based on a maternal report for home deliveries. For children ≤24 mo of age who were born prematurely (gestation <37 wk), age was corrected by subtracting the number of weeks of missed gestation from the current age. A history was taken to assess for symptoms suggesting that the child was not clinically well (cough, shortness of breath, diarrhea, fever, and anorexia); children assessed as being clinically unwell on the basis of these symptoms were excluded from the trial and referred to a stabilization center for further assessment. An appetite test was performed by offering children a small sample of ready-to-use therapeutic food to eat. Children who did not eat at least one-third of a packet (3 teaspoons, 30 g) of ready-to-use therapeutic food after 3 feeding attempts were classified as having poor appetite, excluded from the study, and referred for inpatient management.

A physical examination was then performed. Children were assessed for the following signs of rickets: bow legs, knock knees, windswept deformity of the knees, and proximal myopathy. The child's alertness was assessed: children who were lethargic, apathetic, unconscious, or had seizures were deemed to be nonalert and excluded from the trial. The child's hydration status was assessed: children with a history of recent watery diarrhea associated with eyelid retraction, weak or absent radial pulse, absence of tears, cold peripheries, lethargy, or absence of urinary output were deemed to have severe dehydration and excluded from the trial. Children were assessed for the presence of palmar pallor: those whose palms were very pale, or so pale that they looked white, were deemed to have severe anemia and were excluded from the trial. Children were assessed for the presence of pitting edema: thumb pressure was applied to the tops of the feet for 3 s and pitting edema was judged to be present where a thumb impression remained for a few seconds on both feet. Edema was graded as mild (grade 1, affecting both feet/ankles), moderate (grade 2, affecting both feet, plus lower legs and hands), or severe (grade 3, generalized edema including both feet, plus legs, arms and face). Children with severe (grade 3) pitting edema were

excluded from the trial. Vital signs (temperature, pulse, and respiratory rate) were recorded, and children who were hypothermic or who had hyperpyrexia (axillary temperature $<35^{\circ}\text{C}$ or $>39^{\circ}\text{C}$, respectively) were excluded from the trial. Children with tachypnea (>50 breaths/min for those aged <12 mo, >40 breaths/min for those aged 12–59 mo), chest indrawing, wheeze, or stridor were classified as having a likely acute lower respiratory infection and excluded from the trial. A heel-prick was performed to check for hypoglycemia with the use of a Dextrostix reagent strip: children with a heel-prick glucose concentration of <3 mmol/L were considered to be hypoglycemic and excluded from the trial.

Anthropometric measurements were conducted by outpatient clinic staff who were specifically trained to make these measurements. Their competence in measuring weight, height, and MUAC was assessed and confirmed by the principal investigator. Double measurements were taken by a staff member. If they differed from each other, additional measurements were made until an exact value was replicated. The replicated value was then recorded. MUAC was measured to the nearest 0.1 cm with color-labeled MUAC tape at the midpoint between the olecranon process and the acromion process. Children were weighed to the nearest 10 g unclothed or in very light clothing with a UNISCALE (19), which was adjusted by a standard weight and calibrated to zero before each measurement. For infants and children who could not stand, the UNISCALE was used to measure the mother's weight alone. The mother was then handed the undressed infant or child while standing on the scales, and the combined weight of the mother and infant was measured. The infant or child's weight was calculated as the difference between these 2 readings. The recumbent length of children ≤ 87 cm in height was measured to the nearest 0.1 cm with the use of a length-measuring board with an affixed headrest and a movable foot piece (SECA GmbH & Co. KG, Hamburg, Germany), placed on a flat surface. Children >87 cm in height were measured in the standing position with heels together and without shoes on a horizontal flat plate fixed to the measuring board base. Weight-for-height z scores were calculated according to the WHO child growth standards (20).

Children who were found to be eligible to participate in the trial also underwent a baseline developmental assessment with the use of the standard protocol of the Denver Development Screening Tool II (DDST II) (21), performed by a nurse with specific training in child development or a pediatrician, who was blinded to the participants' allocation. This instrument assesses the ability of children aged ≤ 6 y to perform a range of tasks and allows them to be compared with a standardized population of children of the same age. Tasks are grouped into 4 categories (social contact, fine motor skills, language, and gross motor skills) and include items such as "smiles spontaneously" (performed by 90% of 3-mo-olds), "bangs 2 cubes held in hands" (90% of 13-mo-olds), "speaks 3 words other than dada/mama" (90% of 21-mo-olds), and "hops on one leg" (90% of 5-y-olds). Following a standardized algorithm, children are assessed as having "no delay," "caution" (an intermediate classification), or "delay" in each category. These category assessments are then used to classify global developmental status as normal (no category delayed and no more than one category classified as "caution"), suspect (≥ 2 cautions or ≥ 1 delay), or untestable (based on a specific pattern of refusals). Of note, some patterns of refusals may allow a category assessment but preclude a global

assessment of developmental status according to DDST II algorithms. Where children were classified as having "untestable" global developmental status at screening, developmental assessments were repeated 2 d later; if the global developmental status was still untestable at this point, the assessment was repeated again 2 d after that. With regard to the timing of developmental assessments relative to commencement of ready-to-use therapeutic food and study medication, all children commenced ready-to-use therapeutic food as soon as the diagnosis of uncomplicated severe acute malnutrition was made, but no child was randomised or commenced study medication until the baseline assessment of developmental status was complete.

Randomization and blinding

The random allocation sequence was generated on a Microsoft Excel spreadsheet by a statistician who was independent of the study (Mr. Arslan Chughtai, Rashid Latif Medical Collage, Lahore); a copy was held by the principal investigator (JS), but she did not consult this during the trial. Consecutive numbers from 001 to 200 were assigned to active and placebo groups in a 1:1 ratio. No restrictions (e.g., stratification, block size) were applied. This code was used by the study pharmacy to label active and placebo medication, with a study number assigned to the active and placebo arms, respectively. Participants were enrolled by 4 health workers in the community management of acute malnutrition (CMAM) program and 1 research nurse, who assigned consecutive identification numbers to participants according to the sequence in which they were enrolled. The hospital pharmacy then supplied study medication bearing this identification number. The active and placebo medications were presented identically (syringes of oily solution for oral administration) and had the same appearance and taste. The parents or guardians of all the study participants were blinded to the allocations, as were the health workers, the research nurse, and the pediatrician who enrolled participants and/or performed study assessments.

Interventions

All participants were treated with an 8-wk course of ready-to-use therapeutic food (see **Supplemental Table 1** for composition) provided by the United Nations International Children's Emergency Fund at community centers according to the WHO and national guidelines (1, 22). Ready-to-use therapeutic food was supplied to parents on a weekly basis according to the child's body weight (1.5–5.0 sachets/d, as per Supplemental Table 2) by suitably trained staff who provided parents with information regarding benefits of ready-to-use therapeutic food and advice as to how it should be taken. Participants also received a 7-d course of oral amoxicillin ($60 \text{ mg} \cdot \text{kg}^{-1} \cdot \text{d}^{-1}$ split into 3 daily doses) during the first week of treatment as per the national guidelines (22). Participants randomly assigned to the intervention arm of the trial additionally received 2 oral doses of 200,000 IU (5 mg) of vitamin D₃ (cholecalciferol) in 1 mL olive oil, administered via a plastic syringe at 2 and 4 wk post-initiation of ready-to-use therapeutic food. This solution was manufactured by GT Pharma (Pvt) Ltd Lahore and quality accredited by the Ministry of National Health Services of Pakistan. We elected to give large bolus doses of vitamin D because they have been shown to be safe and

effective in rapidly elevating circulating 25(OH)D concentrations in children (23–25) and can be directly observed, thereby circumventing potential problems with poor adherence. The specific regimen of $2 \times 200,000$ IU at 2 and 4 wk was chosen as this was already being administered locally to children with complicated severe acute malnutrition, and they tolerated it well. Participants randomly assigned to the control arm of the trial received 2 oral doses of placebo (1 mL extra virgin Dalda olive oil) via a plastic syringe at 2 and 4 wk post-initiation of ready-to-use therapeutic food. Study medication was packed into syringes and sealed at the pharmacy in Shahroze Hospital, Dera Ghazi Khan District, by a registered pharmacist. Syringes containing active or placebo medication were labeled with a unique identification number according to the randomization code, as described above, and stored in a dry, cool environment for up to 8 wk as recommended by the manufacturer. Administration of all doses of study medication was directly observed by study staff.

Follow-up

Study participants were given a CMAM enrollment card, and family members were assisted in bringing children for visits to the study outpatient therapeutic program centers. According to standard practice, children were monitored weekly throughout the whole study period at the centers, which provided their ready-to-use therapeutic food diet and assessed them for any medical or nutritional complications, with recording of serious adverse events and referral to a tertiary care hospital if necessary. Parents were encouraged to come to the outpatient centers for any ailments affecting their child, and treatment was free of charge for study children throughout the trial's duration. Anthropometry and developmental assessments were performed at 8 wk post-initiation of ready-to-use therapeutic food: all 8-wk anthropometric assessments were made by CMAM health workers who were blinded to allocation. All but 7 of the 8-wk developmental assessments were conducted by a research nurse or a pediatrician, who was also blinded to allocation. Seven 8-wk developmental assessments were conducted by the principal investigator because of staff absence. A 3-mL blood sample was taken at the 8-wk follow-up from a subset of 116 participants whose parents gave additional consent; this was centrifuged after clotting, and serum samples were aspirated and frozen at -20°C pending biochemical analysis. Sufficient serum for biochemical analyses was available for 90 of the 116 sampled participants.

Outcome measures

The primary outcome measure was the proportion of participants gaining $>15\%$ of their baseline weight at 8 wk post-initiation of ready-to-use therapeutic food (i.e., 6 wk after their first dose of study medication); this outcome was selected as primary on the basis that it represents a key exit criterion for the outpatient therapeutic program for severe acute malnutrition in Pakistan (22). Secondary outcomes were mean weight and mean weight-for-height or -length z score at 8 wk post-initiation of ready-to-use therapeutic food; proportion of participants with delayed development (global, gross motor, fine motor, language, and personal or social) at 8 wk post-initiation of ready-to-use therapeutic food; mean

serum concentrations of 25(OH)D, corrected calcium, albumin, and prealbumin at 8 wk post-initiation of ready-to-use therapeutic food ($n = 90$ subset); and the proportion of participants with serum 25(OH)D concentration ≥ 50 nmol/L (a widely accepted cutoff used to define vitamin D deficiency) (26) at 8 wk post-initiation of ready-to-use therapeutic food ($n = 90$ subset).

Laboratory methods

Serum 25(OH)D concentrations were measured by liquid chromatography tandem mass spectrometry in the Department of Clinical Biochemistry at the Homerton University Hospital National Health Service Foundation Trust, London, UK, which participates in the Vitamin D External Quality Assessment Scheme (www.deqas.org). Serum concentrations of albumin, prealbumin, and calcium were measured in the same laboratory with the use of an Architect ci8200 analyzer (Abbott Diagnostics). Corrected calcium was calculated with the use of the formula:

$$\text{corrected Ca (mmol/L)} = \text{measured Ca (mmol/L)} + 0.020 \times [40 - \text{albumin (g/L)}] \quad (1)$$

Sample size

Assuming that 76% of children in the control arm would gain $>15\%$ of baseline weight at 8 wk (i.e., the minimum standard expected of a CMAM program) (27), we calculated that a total of 158 participants (79/arm) would need to complete follow-up in order to detect a 16% absolute increase (to 92%) in the proportion of children gaining $>15\%$ weight at 8 wk in the intervention arm with 80% power at the 5% significance level; this effect size was selected on the grounds that it would represent a clinically significant improvement in treatment outcome. The number of 158 was inflated to a total of 194 to allow for attrition owing to death and loss to follow-up. No interim analyses were planned or performed.

Statistical methods

Statistical analyses were conducted by original assigned group with the use of Stata/IC version 12.1 (StataCorp). The z scores for anthropometric outcomes were calculated with the use of WHO Anthro v3.2.2 (28). The primary outcome was analyzed by calculation of the RR with 95% CI comparing the proportion of children in each arm who had gained $\geq 15\%$ in weight at 8-wk follow-up against the baseline. The effect of allocation on continuous outcomes that were assessed both at baseline and at the end of the study (e.g., weight and weight-for-height z score at 8 wk) was analyzed with the use of linear regression, adjusting for the baseline value. The effect of allocation on categorical outcome variables that were assessed both at baseline and at the end of the study (e.g., developmental status) were analyzed with the use of generalized linear models with a log link and binomial distribution to yield an RR adjusted for the baseline value with 95% CI and P value (29). Mean values of continuous outcomes measured at 8 wk but not at baseline [e.g., serum concentrations of 25(OH)D, calcium, albumin, and prealbumin] were compared between the active and placebo groups with the use of unpaired Student's t

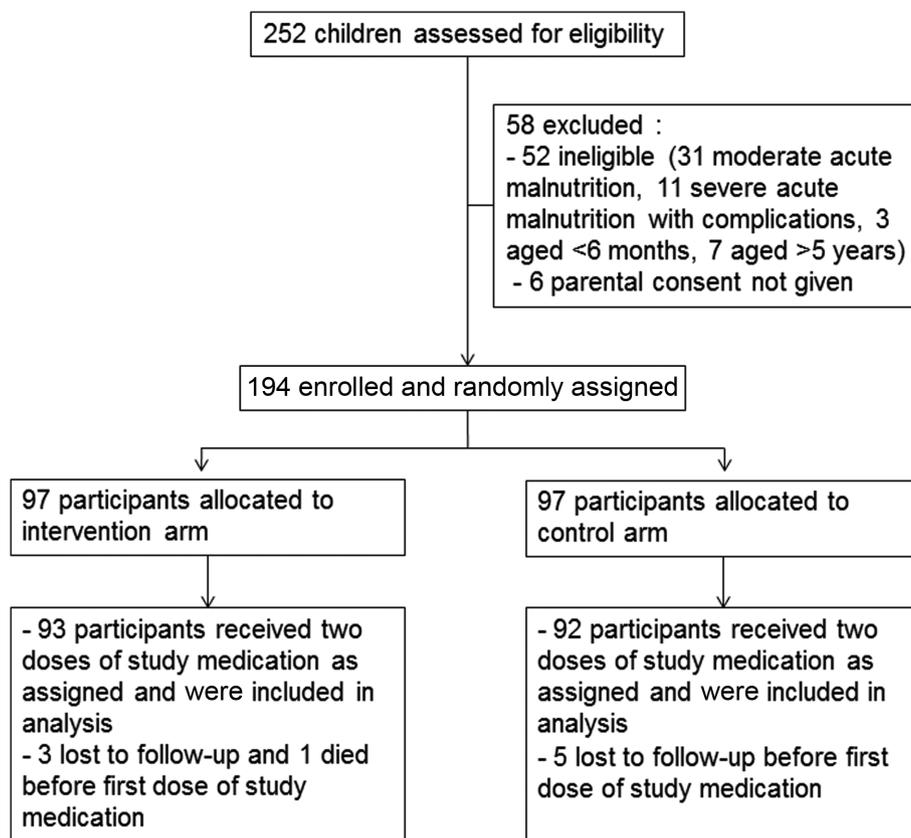


FIGURE 1 Trial profile.

tests to yield a mean difference between study arms with 95% CI for that difference. Statistical significance was inferred where $P < 0.05$. No subgroup analyses were conducted.

RESULTS

Participant flow and recruitment

Figure 1 illustrates participant flow. A total of 252 children were assessed for eligibility to participate in the trial between June 2015 and June 2016: 58 were excluded (52 because they were ineligible, 6 because parental consent was not given) and 194 were randomly assigned, with 97 being allocated to the vitamin D₃ group and 97 receiving the placebo. One child allocated to the vitamin D₃ group died before taking the first dose of study medication (cause of death: dehydration secondary to gastroenteritis), and a further 8 children (3 allocated to vitamin D₃, 5 allocated to placebo) moved away from the study site prior to administration of the first dose of study medication. The remaining 185 participants (93 allocated to vitamin D₃, 92 allocated to placebo) all took both doses of study medication, completed the follow-up and were included in the analysis. The trial ended on the date of the final study visit of the last participant to be randomly assigned.

Baseline characteristics

The clinical and demographic characteristics of the participants included in the analysis were comparable for the

intervention and control groups at baseline (Table 1). Overall, the mean age was 15.4 mo (range 6–58 mo) and 104 out of 185 (56%) participants were female. The mean weight was 5.5 kg (range 2.4–11.7 kg), the mean weight-for-height z score was -3.9 (range -7.0 to -1.0) and mean MUAC was 10.2 cm (range 7.0–12.0 cm). Global developmental status was classified as “untestable” for 34 children at baseline, 19 of whom were untestable 2 d later and 8 were untestable 2 d after that. The proportion of participants with delayed global development at baseline was 108/177 (61.0%). No participant had clinical signs of rickets at baseline.

Efficacy outcomes

The effects of high-dose vitamin D₃ on outcomes at 8 wk post-initiation of ready-to-use therapeutic food are presented in Table 2. The proportion of participants with weight gain $>15\%$ of baseline at 8 wk post-initiation of ready-to-use therapeutic food was not significantly different between participants randomly assigned to vitamin D₃ and those randomly assigned to placebo (84 out of 93 compared with 80 out of 92 respectively, RR: 1.04; 95% CI: 0.94, 1.15, $P = 0.47$; Table 2). However, mean weight-for-height z score and mean weight at 8 wk post-initiation of ready-to-use therapeutic food were both significantly higher in the participants randomly assigned to vitamin D₃ (mean inter-arm difference in weight-for-height z score, adjusted for baseline: 1.07; 95% CI: 0.49, 1.65, $P < 0.001$; mean interarm difference in weight, adjusted for baseline: 0.26 kg; 95% CI: 0.11,

TABLE 1
Baseline characteristics by allocation¹

	Vitamin D ₃ (n = 93)	Placebo (n = 92)
Age, mo	15.7 ± 10.8 ²	15.0 ± 9.6
Age range, mo	6–54	6–58
Proportion female, n/total n (%)	51/93 (54.8)	53/92 (57.6)
Proportion with family income <15,000 Pakistani rupees/mo, n/total n (%)	71/93 (76.3)	57/92 (62.0)
Anthropometry		
Weight, kg	5.9 ± 1.8	5.1 ± 1.5
Weight-for-height z score	−3.8 ± 1.4	−4.1 ± 1.3
Height-for-age z score	−3.9 ± 1.7	−3.7 ± 1.4
Weight-for-age z score	−4.5 ± 1.1	−4.6 ± 1.1
MUAC, cm	10.5 ± 0.8	9.9 ± 1.0
Developmental status		
Proportion with delayed global development, ³ n/total n (%)	53/88 (60.2)	55/89 (61.8)
Proportion with delayed gross motor development, n/total n (%)	37/93 (39.8)	32/92 (34.8)
Proportion with delayed fine motor development, n/total n (%)	35/93 (37.6)	37/92 (40.2)
Proportion with delayed language development, n/total n (%)	31/93 (33.3)	29/92 (31.5)
Proportion with delayed personal or social development, n/total n (%)	59/93 (63.4)	59/92 (64.1)
Proportion with up-to-date vaccination status, ⁴ n/total n (%)	65/93 (69.9)	74/92 (80.4)
Proportion exclusively breastfed up to the age of 6 mo, n/total n (%)	19/93 (20.4)	17/92 (18.5)
Proportion following WHO-recommended complementary feeding practices, ⁵ n/total n %	24/93 (25.8)	21/92 (22.8)

¹MUAC, mid-upper arm circumference.

²Mean ± SD (all such values).

³Global development status was classified as ‘untestable’ at baseline for a total of 8 children (5 allocated to vitamin D₃, 3 allocated to placebo).

⁴Up-to-date according to the schedule of the WHO expanded program on immunization, Pakistan (30).

⁵As defined in ref. (31).

0.41, $P = 0.001$; **Figure 2**). High-dose vitamin D₃ also reduced the proportion of participants with delayed global development at 8 wk (RR adjusted for baseline global developmental status: 0.49; 95% CI: 0.31, 0.77, $P = 0.002$). Analysis of individual DDST II components revealed that allocation to high-dose vitamin D₃ resulted in statistically significant reductions in the proportion of participants having delayed gross motor development (RR adjusted for baseline gross motor developmental status: 0.29; 95% CI: 0.13, 0.64, $P = 0.002$), delayed fine motor development (RR adjusted for baseline fine motor developmental status: 0.59; 95% CI: 0.38, 0.91, $P = 0.018$), and delayed language development (RR adjusted for baseline language developmental status: 0.57; 95% CI: 0.34, 0.96, $P = 0.036$) at the 8-wk follow-up. No statistically significant effect of the intervention was seen on the outcome of personal or social development at 8 wk post-initiation of ready-to-use therapeutic food (RR adjusted for baseline personal or social developmental status: 0.78; 95% CI: 0.58, 1.04, $P = 0.093$). In the subset of 90 participants for whom biochemical analyses were performed, mean end-study serum 25(OH)D concentrations were significantly higher among participants randomly assigned to intervention compared with the control group (99.4 vs. 46.6 nmol/L, mean interarm difference 52.7 nmol/L; 95% CI for difference: 40.3, 65.2 nmol/L, $P < 0.001$). All (45/45) sampled participants randomly assigned to the intervention arm had end-study serum 25(OH)D concentrations >50 nmol/L, as compared with 19/45 (42%) sampled participants randomly assigned to the placebo (RR: 2.37; 95% CI: 1.68, 3.33, $P < 0.001$). The end-study serum 25(OH)D concentration exceeded 125 nmol/L in 12/45 (26.7%) participants randomly assigned to vitamin D. The concentrations ranged from 58 to 195 nmol/L in participants randomly assigned to the intervention arm and from 12 to 75 nmol/L in participants randomly

assigned to the placebo. No statistically significant difference in mean serum concentrations of corrected calcium, albumin, or pre-albumin were seen for participants randomly assigned to the intervention and control arms of the trial at 8 wk post-initiation of ready-to-use therapeutic food.

Adverse events

Only one serious adverse event occurred during this study: one participant died of severe dehydration secondary to acute gastroenteritis. This event occurred after randomization but before any dose of study medication was administered. No actual or suspected adverse reactions arose during the trial.

DISCUSSION

To our knowledge, this is the first randomized controlled trial to investigate the effects of high-dose vitamin D supplementation in children with severe acute malnutrition. Among children with uncomplicated severe acute malnutrition in Pakistan, we found that the administration of 2 oral doses of 200,000 IU (5 mg) of vitamin D₃ in addition to ready-to-use therapeutic food resulted in clinically significant improvements in mean weight and mean weight-for-height z score at 8 wk post-initiation of ready-to-use therapeutic food (6 wk post-initiation of study medication). High-dose vitamin D supplementation also resulted in substantial reductions in the proportion of children with delayed global developmental status, delayed gross and fine motor development, and delayed language development at the end of the study. Despite the relatively high dose of vitamin D administered, no suspected or actual adverse reactions were reported, and no hypercalcemia was observed in a subset of 90 participants for whom end-study results of biochemical analyses were available.

TABLE 2
End-study outcomes by allocation¹

	Vitamin D (<i>n</i> = 93)	Placebo (<i>n</i> = 92)	RR (95% CI)	Mean difference (95% CI)	<i>P</i>
Anthropometric outcomes					
Proportion with weight gain >15% of baseline, <i>n</i> /total <i>n</i> (%)	84/93 (90.3)	80/92 (87.0)	1.04 (0.94, 1.15) ²	—	0.47
Weight, kg	7.50 ± 1.95 ³	6.49 ± 1.58	—	0.26 (0.11, 0.41) ⁴	0.001
Weight-for-height or -length <i>z</i> score	0.15 ± 2.83	-1.22 ± 2.00	—	1.07 (0.49, 1.65) ⁴	<0.001
Developmental outcomes					
Proportion with delayed global development, ⁵ <i>n</i> /total <i>n</i> (%)	19/91 (20.9)	36/91 (39.6)	0.49 (0.31, 0.77) ⁶	—	0.002
Proportion with delayed gross motor development, <i>n</i> /total <i>n</i> (%)	6/93 (6.5)	18/92 (19.6)	0.29 (0.13, 0.64) ⁶	—	0.002
Proportion with delayed fine motor development, <i>n</i> /total <i>n</i> (%)	15/93 (16.1)	28/92 (30.4)	0.59 (0.38, 0.91) ⁶	—	0.018
Proportion with delayed language development, <i>n</i> /total <i>n</i> (%)	12/93 (12.9)	19/92 (20.7)	0.57 (0.34, 0.96) ⁶	—	0.036
Proportion with delayed personal or social development, <i>n</i> /total <i>n</i> (%)	32/93 (34.4)	41/92 (44.6)	0.78 (0.58, 1.04) ⁶	—	0.093
Biochemical outcomes⁷					
Serum 25(OH)D concentration, ⁸ nmol/L	99.4 ± 39.7 [58–195]	46.6 ± 14.1 [12–5]	—	52.7 (40.3, 65.2) ⁹	<0.001
Proportion with serum 25(OH) D ≥50 nmol/L, <i>n</i> /total <i>n</i> (%)	45/45 (100.0)	19/45 (42.2)	2.37 (1.68, 3.33) ²	—	<0.001
Serum corrected calcium concentration, mmol/L	2.30 ± 0.19	2.28 ± 0.26	—	0.02 (-0.08, 0.12) ⁹	0.71
Serum albumin concentration, g/L	38.0 ± 6.4	38.4 ± 5.7	—	0.40 (-2.27, 3.06) ⁹	0.77
Serum prealbumin concentration, g/L	0.17 ± 0.04	0.15 ± 0.05	—	-0.02 (-0.04, 0.00) ⁹	0.11

¹ Study ended at 8 wk post-initiation of ready-to-use therapeutic food, i.e., 6 wk post-initiation of study medication. MUAC, mid-upper arm circumference.

² Unadjusted RR.

³ Mean ± SD (all such values).

⁴ Mean difference from linear regression, adjusting for baseline value.

⁵ End-study global developmental status was classified as “untestable” for a total of 3 children (2 allocated to vitamin D₃, 1 allocated to placebo).

⁶ RR from generalized linear model with a log link and binomial distribution, adjusted for baseline value.

⁷ End-study biochemical outcomes were measured in a subset of 90 participants (45 allocated to each arm of the trial).

⁸ Values are means ± SDs [ranges].

⁹ Mean difference from unpaired Student's *t* test.

Vitamin D supplementation has previously been reported to improve weight gain and growth in children: in a randomized controlled trial conducted in 2079 low-birthweight term infants in New Delhi, India, Trilok Kumar and colleagues (11) reported that a weekly oral dose of 1400 IU of vitamin D₃ improved *z* scores for weight, length, and arm circumference by 0.11–0.12 points at 6 mo. Our study extends this finding to show that, in

a clinically distinct population of children with uncomplicated severe acute malnutrition, administration of a much higher dose of vitamin D was well tolerated and resulted in substantial and clinically meaningful increases in mean weight-for-height or -length of >1 *z* score. In other clinical contexts, vitamin D has been shown to protect against acute infections and accelerate resolution of inflammation (14, 15): both infections and increased

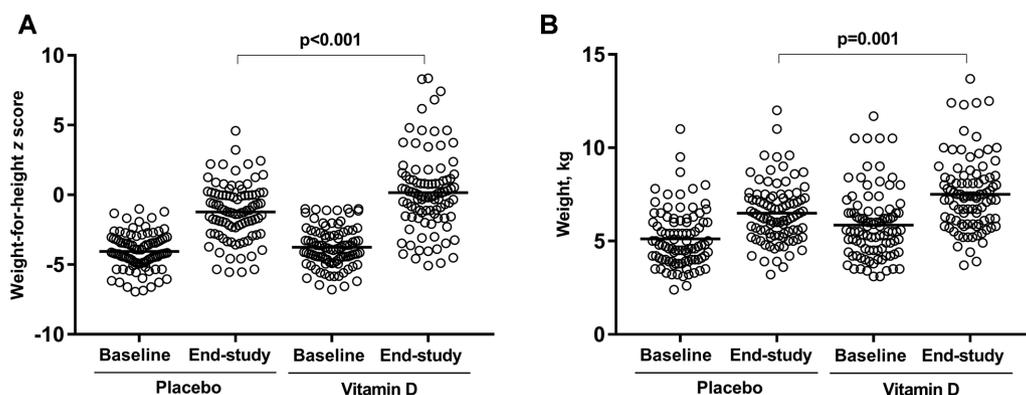


FIGURE 2 Weight-for-height *z* scores (A) and weights (B) by allocation and time point. Lines represent mean values. *P* values for comparison of mean end-study values in children allocated to vitamin D and to placebo are from linear regression, adjusted for baseline values. Data are presented for 92 participants pre/postplacebo and 93 participants pre/postvitamin D.

systemic inflammation are associated with adverse outcome in severe acute malnutrition (16, 17), and it may be that these immunomodulatory actions of vitamin D underlie the improvements in weight gain that we observed.

In keeping with reports of other trials in children being treated for severe acute malnutrition (32, 33), we observed longitudinal improvements in developmental status in both arms of the study. However, the improvements that we observed among participants randomly assigned to high-dose vitamin D₃ were significantly greater than those seen in the control arm. The improvements in gross motor development that we observed in the intervention arm over the control arm likely reflect recognized benefits of vitamin D supplementation for skeletal muscle function (12). However, our finding of a favorable effect of vitamin D supplementation on language development provides novel evidence of neurodevelopmental benefits of vitamin D supplementation in children. This finding complements the results of animal studies demonstrating the importance of vitamin D for brain development (13), and lends weight to the emerging paradigm that vitamin D has important effects on development and functioning of the central nervous system in humans (34). Taken together, our findings suggest that the vitamin D content of current ready-to-use therapeutic food is not optimal for supporting weight gain and development in children with severe acute malnutrition, at least in the population that we studied.

Our study has several strengths. Developmental testing was conducted by well-trained clinical staff with the use of established protocols (21). In order to minimize missing data, they repeated developmental assessments ≤ 2 times in children whose status was initially assessed as being untestable. Administration of study medication was directly observed, ensuring 100% adherence, and the intervention regimen was effective in elevating 25(OH)D concentrations to >50 nmol/L in all participants assigned to take it in whom the concentrations were measured. Rates of loss to follow-up were low.

Our study also has some limitations. We did not conduct a dose-response study; it therefore remains unclear whether a lower dose than we administered would be sufficient to boost weight gain to a similar extent. Although we saw no overt adverse reactions to the high dose of vitamin D administered, biochemical safety monitoring was restricted to analysis of end-study serum concentrations of 25(OH)D and calcium in a subset of 90 participants only. End-study 25(OH)D levels exceeded 125 nmol/L in the 12/45 (26.7%) intervention arm participants in whom they were measured. The possibility of side effects arising with clinical use of this high dose cannot be excluded. Another limitation is that we did not assess vitamin D status at baseline. However, our finding that $>40\%$ of participants in the control arm had end-study circulating 25(OH)D concentrations <50 nmol/L (i.e., despite taking up to 3000 IU vitamin D/d for 8 wk via ready-to-use therapeutic food) indicates that baseline vitamin D status is likely to have been very low in this cohort. The increases in mean weight-for-height or -length that we observed in both study arms were somewhat larger than have been reported in other trials (35, 36) whereas mortality was much lower—likely reflecting the fact that we excluded children with complicated severe acute malnutrition. Accordingly, the proportion of participants gaining $>15\%$ of their baseline weight at 8 wk in the control arm was higher than anticipated, making it difficult to demonstrate an additional benefit of the intervention on the primary outcome. The study duration was

also relatively short, and this precluded an assessment of whether the striking early benefits on anthropometric and developmental outcomes that we demonstrated could be sustained and translated into long-term benefits on growth and neuropsychiatric function.

In summary, we show that administration of high-dose vitamin D in addition to ready-to-use therapeutic food safely and significantly enhanced weight gain and developmental status of children with uncomplicated severe acute malnutrition living in Pakistan. Further trials with a longer follow-up in different settings are needed to explore these promising findings.

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The authors' contributions were as follows—JS, RZ, and MZZ: designed and implemented the trial; MR and PMT: developed and ran the laboratory assays; JS, MB, RS, and ARM: analyzed the data; JS, RS, and ARM: drafted the manuscript; and all authors: critically reviewed and approved the final version. JS is guarantor for the study. None of the authors has a conflict of interest to declare.

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