Weight-for-Height Z-score Gain during Inpatient Treatment and Subsequent Linear Growth during Outpatient Treatment of Young Children with Severe Acute Malnutrition: A Prospective Study from Uganda

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ABSTRACT

Background: Linear catch-up growth after treatment of severe acute malnutrition (SAM) is low, and little is known about the association between ponderal and subsequent linear growth.

Objective: The study assessed the association of weight-for-height z-score (WHZ) gain with subsequent linear growth during SAM treatment and examined its modifiers.

Methods: This was a prospective study, nested in a trial (ISRCTN16454889), among 6–59-mo-old children treated for SAM in Uganda. Weight, total length (TL), and knee-heel length (KHL) were measured at admission, weekly during inpatient therapeutic care (ITC), at discharge, and fortnightly during outpatient therapeutic care (OTC) for 8 wk. Linear regression was used to assess the association between WHZ gain during ITC and linear growth during OTC.

Results: Of 400 children, 327 were discharged to OTC and 290 were followed up for 8 wk. Mean WHZ gains were 0.45 in ITC and 1.24 in OTC, whereas mean height-for-age z-score (HAZ) declined by 0.41 during ITC and increased by 0.14 during OTC. WHZ gain during ITC was positively associated with HAZ, TL, and KHL gains during OTC [regression coefficients (β) (95% CI): 0.12 (0.09, 0.15) z-score; 3.1 (2.4, 3.8) mm and 0.5 (0.1, 0.7) mm, respectively]. The regression coefficients were highest for the middle tertile of WHZ gain with respect to HAZ and TL. Admission diarrhea and low plasma citrulline reduced the association between WHZ gain during ITC and HAZ and TL gain during OTC (P < 0.001). In contrast, pneumonia (P = 0.051) and elevated plasma C-reactive protein (P < 0.001) increased the association with TL gain, but reduced the association with KHL gain (P < 0.001).

Conclusions: Among children admitted with SAM, considerable WHZ gain during ITC was followed by very modest linear catch-up growth during OTC, with no indication of a WHZ gain threshold, above which linear growth was higher. To optimize linear growth in these children, early treatment of infections and conditions affecting the gut may be necessary. Curc Dev Nutr 2021;5:nzab118.

Keywords: stunting, linear growth, severe acute malnutrition, children, Uganda

Introduction

Stunting, defined as a height-for-age z-score (HAZ) below −2 of the median of the WHO child growth standards, affects approximately 144 million children of <5 years old globally (1). Moreover, many more children are affected by some degree of linear growth faltering (2, 3).

Stunting is associated with increased risks of infectious diseases, mortality, reduced cognitive and physical development, adverse...
maternal reproductive outcomes, as well as noncommunicable diseases and reduced productivity in adulthood (2, 4–7). In addition, studies of children with severe acute malnutrition (SAM) have shown that SAM and stunting often co-exist in the same child (4, 8–16), and that >40% of these children are severely stunted (17–19).

While SAM and stunting are individually associated with an increased risk of mortality, children with multiple anthropometric deficits are at a greatly increased risk of mortality (4, 20). However, the current WHO treatment protocols for SAM (21) aim to rapidly restore weight-for-length/height z-score (WHZ) and/or midupper arm circumference (MUAC) deficits (22), with limited attention given to restoration of linear growth, even though the current targets of the World Health Assembly aim to reduce childhood stunting by 40% by 2025 (23). It is even more disturbing that studies of children recovering from SAM have failed to demonstrate catch-up in linear growth (9, 11, 13, 17, 18, 24–27).

Being wasted has recently been shown to increase the risk of subsequent stunting by 3-fold, while being stunted increases the risk of subsequent wasting by 1.5-fold (28). This highlights the need to better understand the relation between ponderal and linear growth in children with SAM. In addition, ponderal and linear growth is influenced by a number of dietary and environmental factors as well as infectious diseases (29, 30). Thus, knowing which factors modify the associations between WHZ and subsequent linear growth among children treated for SAM could help identify those at high risk of poor linear growth, for whom more attention may be needed.

The association between growth in weight and length in children with SAM has been studied before, but the findings are inconsistent (11, 12, 17, 18). In a study of hospitalized Jamaican children with SAM, Walker and Golden (11) showed that two-thirds of the children reached a weight-for-length of 85% of National Center for Health Statistics (NCHS) median before linear growth occurred and that most of the children reached a critical threshold WHZ of −1.3 prior to growth in length. However, concurrence of growth in both WHZ and HAZ has been reported in Bangladesh (12), while in Kenya, increase in WHZ was not associated with linear growth (17).

Knemometry is a method that measures knee-heel length (KHL), including length of the tibia and the soft tissues at both ends. It is a precise and sensitive measure of linear growth over short periods of time, detecting smaller differences with less variation than total length (TL) (31). Apart from a study of Bangladeshi hospitalized children with SAM that found a significant correlation between KHL growth and change in WHZ over time (12), data on association of WHZ and subsequent KHL growth in children with SAM remain limited.

The objective of this study was to assess the association of WHZ gain during inpatient therapeutic care (ITC) with subsequent linear growth during outpatient therapeutic care (OTC) and to identify possible modifiers. The main hypothesis was that children need to gain in WHZ before linear growth can take place, and that the association between WHZ gain and subsequent linear growth is modified by sex, edema, inflammation, or gut function at admission. We also hypothesized that these factors primarily modify the association with growth of the lower leg.

**Methods**

**Study design, setting, and population**

The study was a prospective cohort nested in a randomized clinical trial (www.isrctn.com, ISRCTN16454889), conducted among 400 children with SAM at Mwanamugimu Nutrition Unit (MNU), Mulago National Referral Hospital, Kampala, Uganda, from March 2014 to October 2015.

**Inclusion and exclusion criteria**

Children aged 6–59 mo old with complicated SAM, whose caregivers gave written informed consent were included. Complicated SAM was defined as WHZ <−3 or MUAC <11.5 cm or bipedal pitting edema, plus any medical complications requiring hospitalization as per WHO guidelines (21).

Those in shock, severe respiratory distress, weighing <4.0 kg, having significant disabilities that affect response to nutritional therapy, as well as those who had been admitted with SAM 6 mo prior to the study were excluded.

**Patient management**

Patients were managed based on the WHO (21) and the Ugandan integrated management of acute malnutrition (IMAM) protocols (32), as reported elsewhere (33–36). Briefly, children received therapeutic diets consisting of F-75, ready-to-use-therapeutic food (RUTF; Plumpy’nut®) or F-100 (Nutriset) and intravenous antibiotics, commonly ampicillin and gentamycin. During the stabilization phase, F-75 feeds were given at 100–130 mL/kg per day based on severity of edema. Where applicable, breastfeeding in-between the therapeutic feeds was supported. Rehydration Solution for the Malnourished (ReSoMal; Nutriset) was given to those with diarrhea based on WHO protocol (21).

Once a child was stabilized, feeds were transitioned from F-75 to RUTF or F-100 according to WHO recommendations. During the rehabilitation phase of ITC, children received RUTF or F-100, plus a nutritious local dish (kitobero). The feeds were increased based on the child’s body weight and appetite, and provided between 150 to 200 kcal/kg per day. The children who met the WHO 2013 (21) criteria for discharge were given a 2-wk supply of RUTF and transferred to OTC. Caregivers and their children returned for follow-up at 2, 4, 6, and 8 wk. During follow-up, for each child, a clinical examination was conducted, anthropometry taken, and RUTF refilled. Discharge criteria from OTC was based on WHO 2013 guidelines (21), as detailed elsewhere (36).

**Data collection**

At admission, the child’s sociodemographic information and breastfeeding and medical history were obtained. A study nurse collected data on the household and, where possible, on the mothers’ age, education, occupation, and marital status. The study nurse also collected data on food insecurity using the Household Food Insecurity Access Scale (HFIAS) (37). A study medical doctor performed a full physical examination. Anthropometry during ITC and OTC was measured by nutritionists who were specifically recruited and trained by the parent trial management team. A caregiver was requested to completely or partially undress the child depending on the nature of the measurements to be taken. Child body weight, MUAC, and TL were measured in triplicate at admission, weekly during hospitalization, at discharge, and during OTC visits in accordance with WHO guidelines (21), and KHL was...
measured 5 times at the same time points. Single body-weight measurements were also taken between 07:00 and 08:00 h during ITC. Body weight was measured to the nearest 100 g using a digital scale (Seca 813; Hamburg, Germany). MUAC was assessed to the nearest 1 mm using standard non-elastic color-coded tapes for children aged <5 y (Child 11.5 red/pac-50; UNICEF). Measurements were performed on the left arm. TL (encompassing both recumbent and standing height) was measured using an infant length board (Infant/Child Shorr-Board®; Maryland, USA) to the nearest 1 mm (standing height was measured for children ≥24 mo of age). KHL was measured on the left lower leg with a digital hand-held caliper with a resolution of 0.01 mm (Mitutoyo, Germany) mounted with knee and heel caps cast in hard plastic (38). The set of 5 measurements, each aimed at the same position (highest spot of lateral femoral condyle on the knee and under the heel straight down from lateral malleolus of fibula) and same applied pressure, was performed and then a print-out of statistical calculations (mean, SD, SE, minimum and maximum values) was instantly available by use of a mobile field printer attached to the knemometer. If the SD was >1 mm, the set of 5 measurements was repeated. Mothers’ anthropometry was measured on admission only. Triple body-weight measurements were taken using a digital scale (Seca 813; Hamburg, Germany) to the nearest 100 g and height, using an adult height board (adult Shorr-Board®; Maryland, USA) to the nearest 1 mm, with no shoes and extra clothes. The average was calculated in case of repeated measurements. WHO Anthro version 3.2.2 (15) was used to calculate WHZ and HAZ. BMI for the mother was calculated as weight (kg)/height squared (m²) (39).

Study pediatricians and nutritionists were responsible for clinical and nutritional assessment of the patients, respectively, and jointly decided on patient management.

Laboratory tests
Four milliliters of venous blood was collected into EDTA-treated Vacutainer tubes (Becton Dickinson; Franklin lakes, NJ USA). Samples for complete blood counts were analyzed using a Coulter counter at the Uganda Cancer Institute laboratory. HIV sero-status was assessed at the MNU side laboratory using Determine HIV-1/2 (Abbott Laboratories USA) rapid tests and HIV-1/2 Stat-Pak Dipstick Assay kit for children aged >18 mo. For those <18 mo of age, their HIV status was confirmed using an HIV DNA/polymerase chain reaction (PCR) test done at Baylor HIV clinic. Plasma was obtained by centrifuging at 1300–2200 × g at ambient temperature for 10 min, and stored at −80°C prior to shipment on dry ice to the University of Copenhagen, Denmark. Plasma C-reactive protein (CRP) was analyzed by the high-sensitivity kit on an ABK Pentra 400 (Horiba; Montpellier, France). Detection of plasma citrulline has been described in detail elsewhere (40). Briefly, the LC-MS method (41) was used. Samples were processed with Sirocco protein precipitation plate (Waters) and separated on an ACQUITY UPLC HSS T3 Column (Waters) using an ultra-performance LC in tandem with triple quadrupole detector MS. 1-Citrulline-4,4,5,5-d4 (Sigma-Aldrich) was used as an internal standard. Quantification of citrulline was carried out using QuanLynx (Waters).

Ethical issues
The study followed the Helsinki Declaration and the Ugandan guidelines. Ethical approval was obtained from Makerere University School of Medicine Research Ethics Committee, the Uganda National Coun-cil for Science and Technology, as well as Uganda National Drug Authority and a consultative approval from the Danish National Committee of Health Research Ethics. All parents or legal guardians provided written informed consent before their child was enrolled in the study. Caregivers were given oral and written detailed explanations regarding the study and procedures to be conducted. Regardless of participation in the study, all children received standard routine medical and nutritional therapy. Caregivers received a modest transport compensation.

Study outcomes
The main study outcomes were gains in HAZ, TL, and KHL from discharge to 8 wk during OTC. Other outcomes were weight gain during OTC, plus HAZ, TL, and KHL gain during ITC.

The main exposure variable was WHZ gain during ITC (from admission to discharge). Other exposures of interest were WHZ at admission, WHZ at discharge, age, sex, and HIV status, as well as edema, pneumonia, diarrhea, plasma CRP, and citrulline at admission.

Gains in TL, KHL, WHZ, and HAZ during ITC or OTC were calculated as assessments at discharge minus assessments at baseline or assessments at 8 wk minus assessments at discharge, respectively. Gains in TL, KHL, WHZ, and HAZ per week during ITC or OTC were calculated as assessments at discharge minus assessments at baseline or assessments at 8 wk minus assessments at discharge/number of weeks from baseline to discharge or from discharge to 8 wk, respectively. Weight gain (grams) during ITC was calculated as (discharge weight − minimum weight) in kilograms × 1000. Because all children had no edema or diarrhea and/or dehydration at discharge, weight gain (grams) during OTC was calculated as (weight at 8 wk − discharge weight) in kilograms × 1000. Weight gain (grams/kilograms per day) during ITC or OTC was calculated as weight gain (grams)/minimum weight or discharge weight (kilograms)/number of days from minimum weight to discharge or from discharge to 8 wk, respectively.

Data handling and statistical analysis
Data were double-entered into Epidata version 3.1 and analysis was performed using R version 3.5.1 (R Core Team, 2017), with the extension packages plyr, dplyr, and multcomp. Baseline characteristics were summarized using means ± SDs for normally distributed continuous variables or median (IQR) for non-normally distributed continuous variables, and percentages (%) for categorical variables. Both for ITC and OTC, a 2-sample t test was used to examine differences in mean gain in weight, TL, KHL, WHZ, and HAZ between sex and edema at admission. Chi-square test was used to compare the percentage of KHL relative to TL at baseline, discharge, and end of follow-up between sex and edema at admission. Associations between WHZ gain during ITC, WHZ at admission, or WHZ at discharge and HAZ, TL, and KHL gain during OTC were investigated using linear regression. In addition, these associations were investigated within strata defined by tertiles of WHZ gain during ITC, WHZ at admission, and WHZ at discharge. Both overall and strata-specific analyses were controlled for age, sex, edema at admission, and HIV status. Furthermore, modifiers of the associations between WHZ gain during ITC and HAZ, TL, and KHL gain during OTC were investigated by fitting linear regression models that included interaction terms between WHZ gain during ITC and each of the following variables: sex, edema, pneumonia, diarrhea, plasma CRP, and
### TABLE 1 Baseline characteristics of 400 children admitted with severe acute malnutrition

| Characteristic                              | n    | Values                        |
|---------------------------------------------|------|-------------------------------|
| **Child**                                   |      |                               |
| Age, mo                                     | 400  | 15.0 (11.2; 19.2)             |
| Male sex                                    | 400  | 230 (58%)                     |
| Midupper arm circumference, cm              | 392  | 11.6 ± 1.5                    |
| Total length, cm                            | 398  | 71.2 ± 6.2                    |
| Knee-heel length, mm                        | 380  | 186.8 (173.9; 202.6)          |
| Weight, kg                                  | 399  | 6.7 (5.7–7.9)                 |
| Weight-for-length/height z-score            | 387  | −2.9 (−3.7; −1.5)             |
| Length/height-for-age z-score               | 387  | −3.1 ± 1.4                    |
| Currently breastfeeding                      | 374  | 54 (14%)                      |
| Edema present                               | 399  |                               |
| No                                          | 138  | 138 (35%)                     |
| Yes                                         | 261  | 261 (65%)                     |
| Diarrhea                                    | 400  | 241 (60%)                     |
| Pneumonia                                   | 400  | 68 (17%)                      |
| HIV status                                  | 368  |                               |
| Positive                                    | 43   | 12%                           |
| Negative, exposed                           | 72   | 20%                           |
| Negative                                    | 253  | 69%                           |
| Plasma C-reactive protein                   | 352  |                               |
| < 10 mg/L                                   | 134  | 38%                           |
| ≥ 10 mg/L                                   | 218  | 62%                           |
| Hemoglobin, g/dL                            | 298  | 8.9 (7.8; 10.1)               |
| Plasma citrulline                           | 296  |                               |
| < 10 μmol/L                                 | 235  | 79%                           |
| ≥ 10 μmol/L                                 | 61   | 21%                           |
| **Mother**                                  |      |                               |
| Age, y                                      | 356  | 24.0 (21.0; 28.0)             |
| BMI, kg/m²                                   | 334  | 22.7 (20.9; 25.3)             |
| Education                                   | 385  |                               |
| Primary                                     | 181  | 47%                           |
| Secondary or higher                         | 153  | 40%                           |
| HIV positive                                | 340  | 109 (32%)                     |
| Household                                   | 389  |                               |
| Household Food Insecurity Access Score²     | 5.8 ± 7.0 |

¹Values are number of children with data and medians (IQR) or means ± SDs or n (%).
²A measure of food insecurity in the household in the past 4 wk on a scale from 0 to 27; the higher the score, the more food insecure the household has been.

citrulline at admission, controlled for age, sex, edema at admission, and HIV status. P values were regarded as statistically significant if <0.05.

### Results

Of the 400 children enrolled, the median (IQR) age was 15.0 (11.2, 19.2) mo, 42% were female, and 65% presented with edema (Table 1). Of these, 293 (73%) were followed up at 8 wk, of whom 290 (99%) were included in the analysis of outcomes (Figure 1).

During ITC, the children had a mean (± SD) weight gain of 719 (± 501) g or 6.6 (± 5.0) g/kg/d (Table 2). The weight gain was lower in children with edema at admission. The mean gains in TL and KHL were slightly negative and lower in those with edema at admission. During OTC, the mean (± SD) weight gain of 1177 (± 796) g or 3.1 (± 2.2) g/kg per day was accompanied by a 19-mm gain in TL, of which 8 mm was KHL. There was no difference in weight, TL, KHL, WHZ, and HAZ gain by sex or edema at admission. The gains in weight and length translated into a 0.45 increase in WHZ and a 0.41 decrease in HAZ during ITC and a 1.24 increase in WHZ and 0.14 increase in HAZ during OTC, respectively (Table 3). Figure 2 shows weekly (in ITC) and fortnightly (in OTC) changes in absolute WHZ and HAZ. Mean absolute WHZ decreased from approximately −2.62 z-score to approximately −2.90 z-score after 3 wk in ITC, while mean absolute HAZ decreased from approximately −3.09 z-score to approximately −3.45 z-score (Figure 2A). In contrast, during OTC, mean absolute WHZ increased steadily from approximately −2.07 z-score at week 0 (discharge) and peaked at approximately −0.82 z-score after 8 wk, and HAZ decreased slightly from approximately −3.55 z-score to approximately −3.39 z-score (Figure 2B). At baseline, discharge, and end of follow-up, KHL comprised 27% of TL, with no differences by sex or edema at admission (P > 0.7; data not shown).

### Association between ponderal and subsequent linear growth

As shown in Table 4, after adjusting for age, sex, edema at admission, and HIV status, overall WHZ gain in ITC was positively associated with HAZ, TL, and KHL gain during OTC (P < 0.001). The regression
coefficients reflect that, for each 1-unit higher WHZ gain during ITC, there was a 0.12-unit higher increase in HAZ, corresponding to 3.1-mm higher increase in TL, of which 0.5 mm was KHL gain during OTC. When stratified by tertile, the associations were again positive among those in the lower tertile. With regard to the middle and upper tertiles, there were positive associations with HAZ and TL gain during OTC, and the regression coefficients were higher among those in the middle tertile than in the upper tertile. In contrast, WHZ at admission (overall and tertiles) was negatively associated with all the 3 length measurements ($P < 0.001$). There were no associations between overall WHZ at discharge and linear growth during OTC. However, there were positive associations with TL gain among children in the lower tertile, and with HAZ and TL gain among those in the middle and upper tertiles. Unadjusted analyses are shown in Supplemental Table 1.

### Discussion

This study found that there was minimal change in HAZ during SAM treatment. Yet, there was a positive association between WHZ gain during ITC and subsequent linear growth during OTC, but there was no indication of a WHZ gain above which there was accelerated linear growth. There was a relatively large KHL gain during OTC (41% of TL gain). Admission diarrhea and low plasma citrulline reduced the association between WHZ gain during ITC and HAZ and TL gain during OTC. In contrast, pneumonia and elevated plasma CRP increased the association with TL gain but reduced the association with KHL gain.

### Ponderal and subsequent linear growth

Overall WHZ gain during ITC was positively associated with HAZ, TL, and KHL gain during OTC. Furthermore, similar associations with gains in all 3 length measurements were seen among those in the lower tertile of WHZ gain ($ \leq 0$). However, among those in the middle and upper tertiles with WHZ gain $> 0$, positive associations were seen with HAZ and TL only, indicating that the greater the WHZ gain during ITC, the greater the subsequent linear growth of the trunk, but not KHL, among children in these tertiles. Similar to results of the current study, 2 studies in Jamaica and Niger found that recovery in WHZ precedes...
TABLE 2  Weight, length, and knee-heel length gain during in- and outpatient therapeutic care among children admitted with severe acute malnutrition, both overall and stratified by sex and edema at admission\(^1\)

| Weight gain | Inpatient therapeutic care | | | Outpatient therapeutic care | | |
|---|---|---|---|---|---|---|
| | n | g | P | n | g/kg per day | P | n | g | P | n | g/kg per day | P |
| Total | 326 | 719 ± 501 | | 325 | 6.6 ± 5.0 | | 291 | 1177 ± 796 | | 290 | 3.1 ± 2.2 | |
| Sex\(^2\) | | | | | | | | | | | | |
| Male | 192 | 727 ± 453 | | 191 | 6.5 ± 4.3 | | 173 | 1153 ± 845 | | 172 | 3.0 ± 2.3 | |
| Female | 134 | 708 ± 562 | | 134 | 6.8 ± 5.8 | | 118 | 1212 ± 716 | | 118 | 3.2 ± 2.1 | |
| Edema\(^2\) | | | | | | | | | | | | |
| No | 107 | 791 ± 522 | | 107 | 8.0 ± 5.3 | | 92 | 1105 ± 759 | | 92 | 3.1 ± 2.3 | |
| Yes | 219 | 684 ± 487 | | 218 | 5.9 ± 4.6 | | 199 | 1211 ± 811 | | 198 | 3.0 ± 2.2 | |

| Total length gain | Inpatient therapeutic care | | | Outpatient therapeutic care | | |
|---|---|---|---|---|---|---|
| | n | mm | P | n | mm/wk | P | n | mm | P | n | mm/wk | P |
| Total | 323 | -5.3 ± 12.5 | | 322 | -2.2 ± 6.3 | | 291 | 19.3 ± 14.1 | | 290 | 2.4 ± 1.7 | |
| Sex\(^2\) | | | | | | | | | | | | |
| Male | 190 | -5.4 ± 11.1 | | 189 | -2.3 ± 5.3 | | 172 | 19.7 ± 13.7 | | 171 | 2.4 ± 1.7 | |
| Female | 133 | -5.1 ± 14.2 | | 133 | -2.1 ± 7.5 | | 119 | 18.8 ± 14.6 | | 119 | 2.3 ± 1.8 | |
| Edema\(^2\) | | | | | | | | | | | | |
| No | 219 | -2.2 ± 10.7 | | 218 | -1.1 ± 4.9 | | 92 | 18.6 ± 13.9 | | 92 | 2.3 ± 1.7 | |
| Yes | 104 | -6.7 ± 13.0 | | 104 | -2.8 ± 6.8 | | 199 | 19.7 ± 14.2 | | 198 | 2.4 ± 1.7 | |

| Knee-heel length gain | Inpatient therapeutic care | | | Outpatient therapeutic care | | |
|---|---|---|---|---|---|---|
| | n | mm | P | n | mm/wk | P | n | mm | P | n | mm/wk | P |
| Total | 315 | -0.1 ± 5.8 | | 314 | 0.0 ± 3.0 | | 279 | 8.0 ± 5.1 | | 278 | 1.0 ± 0.6 | |
| Sex\(^2\) | | | | | | | | | | | | |
| Male | 183 | 0.2 ± 6.9 | | 182 | 0.2 ± 3.6 | | 165 | 8.1 ± 4.9 | | 164 | 1.0 ± 0.6 | |
| Female | 132 | -0.4 ± 3.8 | | 132 | -0.2 ± 1.9 | | 114 | 7.7 ± 5.5 | | 114 | 1.0 ± 0.7 | |
| Edema\(^2\) | | | | | | | | | | | | |
| No | 105 | 1.3 ± 3.0 | | 105 | 0.5 ± 1.6 | | 89 | 7.7 ± 5.0 | | 89 | 0.9 ± 0.6 | |
| Yes | 210 | -0.7 ± 6.7 | | 209 | -0.2 ± 3.5 | | 190 | 8.1 ± 5.2 | | 189 | 1.0 ± 0.6 | |

\(^1\)Values are means ± SDs unless otherwise indicated. The median (IQR) duration of in- and outpatient therapeutic care was 17 (12–22) and 56 (42–58) days, respectively; the latter was predetermined by the parent trial.

\(^2\)P values were derived by using a 2-sample t test.
TABLE 3  Weight-for-height and height-for-age z-score gain during in- and outpatient therapeutic care among children admitted with severe acute malnutrition, overall and stratified by sex and edema at admission

|                          | Inpatient therapeutic care | Outpatient therapeutic care |
|--------------------------|-----------------------------|-----------------------------|
|                          | n  | z-score | P   | n  | z-score | P          | n  | z-score | P          |
| Weight-for-height z-score gain | n  |        |     | n  |        |             | n  |        |             |
| Total                    | 323| 0.45 ± 1.04 | 0.660 | 322| 0.18 ± 0.45 | 0.814 | 290| 1.24 ± 1.13 | 0.733 | 289| 0.15 ± 0.14 | 0.694 |
| Sex²                    |    |          |     |    |          |             |    |          |             |
| Male                    | 190| 0.47 ± 0.99 | 0.660 | 189| 0.19 ± 0.42 | 0.814 | 172| 1.22 ± 1.22 | 0.733 | 171| 0.15 ± 0.15 | 0.694 |
| Female                  | 133| 0.41 ± 1.10 | 0.660 | 133| 0.18 ± 0.49 | 0.814 | 118| 1.27 ± 0.98 | 0.733 | 118| 0.16 ± 0.12 | 0.694 |
| Edema²                  |    |          |     |    |          |             |    |          |             |
| No                      | 105| 0.98 ± 0.88 | < 0.001 | 105| 0.40 ± 0.36 | < 0.001 | 92 | 1.29 ± 1.15 | 0.649 | 92 | 0.16 ± 0.14 | 0.722 |
| Yes                     | 218| 0.19 ± 1.01 | < 0.001 | 217| 0.08 ± 0.44 | < 0.001 | 198| 1.22 ± 1.12 | 0.649 | 197| 0.15 ± 0.14 | 0.722 |
| Height-for-age z-score gain | n  |        |     | n  |        |             | n  |        |             |
| Total                   | 324| −0.41 ± 0.47 | 0.685 | 323| −0.16 ± 0.22 | 0.541 | 291| 0.14 ± 0.51 | 0.172 | 290| 0.02 ± 0.06 | 0.172 |
| Sex²                   |    |          |     |    |          |             |    |          |             |
| Male                   | 190| −0.42 ± 0.45 | 0.685 | 189| −0.17 ± 0.20 | 0.541 | 172| 0.17 ± 0.52 | 0.172 | 171| 0.02 ± 0.06 | 0.172 |
| Female                 | 134| −0.40 ± 0.51 | 0.685 | 134| −0.15 ± 0.25 | 0.541 | 119| 0.09 ± 0.49 | 0.172 | 119| 0.01 ± 0.06 | 0.172 |
| Edema²                |    |          |     |    |          |             |    |          |             |
| No                     | 105| −0.33 ± 0.42 | 0.027 | 105| −0.13 ± 0.19 | 0.071 | 92 | 0.07 ± 0.51 | 0.100 | 92 | 0.01 ± 0.06 | 0.092 |
| Yes                    | 219| −0.45 ± 0.49 | 0.027 | 218| −0.18 ± 0.24 | 0.071 | 199| 0.18 ± 0.50 | 0.100 | 198| 0.02 ± 0.06 | 0.092 |

1 Values are means ± SDs unless otherwise indicated. The median (IQR) duration of in- and outpatient therapeutic care was 17 (12–22) and 56 (42–58) days, respectively, but the latter was predetermined by the parent trial.
2 P values were derived by using a 2-sample t test.
HAZ gain in children treated for SAM (11, 18). In the Jamaican study, among a subgroup mainly consisting of those who were non-edematous and more severely stunted at baseline, it was found that linear growth started after the majority of the children had attained a minimum weight-for-length of 85% of the NCHS median. The same study also found minimal change in HAZ during rehabilitation (11). Similarly, the Niger study of children recovering from wasting (non-edematous SAM) found that nutritional recovery (WHZ ≥−2 or MUAC ≥12.5 cm) preceded gain in HAZ in 77% of those who had catch-up in linear growth. They also demonstrated that, during nutritional rehabilitation, there is a rapid increase in WHZ accompanied by a decline in HAZ and, after rehabilitation, there is a slower increase in WHZ as well as a slower decline in HAZ (18). Absence of a clear threshold of WHZ gain at which there is a start of growth in HAZ has also been reported in 2 other studies of children with SAM in Bangladesh and Kenya (12, 17). However, WHZ and HAZ gains were measured concurrently, unlike in our study. Yet, the Kenyan study (17) found that, between enrollment (after the stabilization phase of ITC) and 1 mo of OTC treatment, WHZ had the largest increase, whereas HAZ had the largest decrease, also indicating that WHZ gain takes precedence over HAZ gain.

On the other hand, the positive association with subsequent TL gain observed in this study concurs with results of a study of 127 Jamaican stunted children, showing that WHZ gain was positively associated with subsequent gain in height (43). However, the regression coefficients were higher than what was seen in this study, perhaps because of the differences in study populations. The Jamaican study (43) involved only stunted children who were not severely acutely malnourished.
Further, in agreement with this study, Doherty et al. (12) found that KHL gain is positively correlated with WHZ gain in Bangladeshi children recovering from SAM. The authors suggested that KHL gain initially behaves as a ponderal index. However, children in the Bangladeshi study received intensive inpatient nutritional rehabilitation for 15 d and had their WHZ and HAZ measured concurrently (after every 15 d), unlike in this study, where WHZ gain in ITC was associated with KHL gain during OTC. Knemometry has been shown to be a more sensitive measure of linear growth over short periods than measurement of TL (31). As such, the gain in KHL observed in the Bangladeshi study (12) may have been mediated by early recovery in WHZ following the intensive nutritional treatment that the children received during hospitalization. In addition, measurement of KHL gain involves measuring changes in the length of the tibia and fibula plus changes in the soft tissues covering these (31). Thus, changes in tissue edema as well as fat deposition in the suprapatellar and heel-fat pads that take place during nutritional rehabilitation are likely to influence KHL growth.

Furthermore, this study has shown that, during ITC, there is a decline in HAZ, TL, and KHL, with a higher decline seen in those with edema at admission. In contrast, during OTC, there is an increase in all 3 length measurements, with no difference by edema at admission. This finding is quite unexpected as it is often believed that children cannot lose length. This does not seem to be due to measurement error because triple length measurements were taken during both ITC and OTC. However, loss of edema and nearly no fat deposition during ITC may have caused the observed apparent decrease in all 3 length measurements. This finding concurs with those of a study of children admitted with SAM in Jamaica, in which a decrease in HAZ at discharge was reported in a subgroup of those with kwashiorkor (edematous SAM) (11). Likewise, in Kenya, Ngari et al. (17) reported HAZ loss after 1 mo of follow-up in children treated for SAM.

The mechanisms behind the relation between growth in weight and length are unclear, but some studies have reported involvement of leptin (44). In a study of children with mild malnutrition [defined as weight-for-height between 90% and 80% of the median according to Waterlow criteria (45)], Büyükgözü et al. (44) found a much higher mean leptin concentration in children who showed catch-up in linear growth compared with those who did not, despite the significant weight gain seen in both groups. Moreover, studies of children with SAM in Kenya and Uganda have shown that leptin concentrations are low at admission (46, 47) , but increase relative to treatment period (46). Thus, the increased stores of leptin-producing fat cells during recovery from SAM may be one mechanism through which sufficient weight gain could increase bone and linear growth.

### Modifiers of associations between ponderal and linear growth

While pneumonia does not modify the association between WHZ gain during ITC and HAZ gain during OTC, it tends to increase the association (nonsignificantly) for TL gain, but reduces it for KHL gain during OTC. Therefore, with pneumonia, the body seems to sacrifice knee-heel growth to maintain trunk growth. Interestingly, we see the same pattern for elevated plasma CRP. This is not surprising, since pneumonia precipitates an acute-phase response (48). Data on modifiers of the relation between weight gain during ITC and subsequent linear growth during OTC in children with SAM are rare. In a recent review, Millward (49) reported that inflammation inhibits endochondral ossification through the action of mediators such as proinflammatory cytokines, the activin A-follistatin system, glucocorticoids, and fibroblast growth factor
TABLE 5

| Inpatient therapeutic care | Height-for-age z-score gain | Total length gain, mm | Knee-heel length gain, mm |
|---------------------------|----------------------------|-----------------------|--------------------------|
|                           | z-score gain during ITC (discharge value at admission) and HIV status. CRP, C-reactive protein. | Pn (95% CI) | z-score gain during OTC | P (95% CI) | Pn (95% CI) |
| Sex (male vs. female)     | 223 | 0.10; <0.06 | 0.001 | 223 | 2.76 (2.20) | <0.001 | 212 | 0.66 (0.36) | <0.001 | 0.764 |
| Edema (vs. no edema)      | 223 | 0.04 (0.02; 0.07) | <0.001 | 223 | 1.92 (1.18; 2.66) | <0.001 | 212 | 0.89 (0.59) | <0.001 | 0.001 |
| Pneumonia (vs. no pneumonia) | 223 | 0.02 (0.01; 0.03) | <0.001 | 223 | 0.74 (0.39) | <0.001 | 212 | 0.48 (0.23) | <0.001 | 0.001 |
| Diarrhea (vs. no diarrhea) | 223 | 0.04 (0.02; 0.07) | <0.001 | 223 | 1.79 (1.26; 2.33) | <0.001 | 212 | 0.66 (0.36) | <0.001 | 0.001 |
| Elevated plasma CRP (vs. normal) | 211 | 0.10 (0.08; 0.13) | <0.001 | 211 | 2.81 (2.22; 3.39) | <0.001 | 202 | 0.30 (0.19) | <0.001 | 0.001 |
| Low plasma citrulline (vs. normal) | 223 | 0.04 (0.03; 0.07) | <0.001 | 223 | 2.87 (2.34; 3.41) | <0.001 | 212 | 0.50 (0.25; 0.75) | <0.001 | 0.001 |

1Values are shown as numbers of children per analysis, differences in regression coefficients (Δβ) and corresponding 95% CIs and P-values for test of no difference in regression coefficients between correlates and weight-for-height z-score gain during inpatient therapeutic care (discharge value at admission) and height-for-age z-score and total and knee-heel length gain during outpatient therapeutic care. 2Defined as plasma CRP ≥10 mg/L. 3Defined as plasma citrulline <10 μmol/L.
Our study was conducted at a national referral hospital, where patients usually present with advanced disease. Thus, our findings may not be applicable in settings where children are less ill. Finally, we also considered it a limitation that the follow-up was only 8 wk.

Conclusions
Among children admitted with SAM, considerable WHZ gain during ITC was followed by very modest linear catch-up growth during OTC, and there was no indication of a WHZ gain threshold above which there was accelerated linear growth. Also, WHZ gain during ITC was positively associated with linear growth during OTC, and the regression coefficients were highest for the middle tertile of WHZ gain with respect to HAZ and TL gain. Moreover, admission diarrhea and low plasma citrulline reduced the association between WHZ gain during ITC and HAZ and TL gain during OTC, whereas pneumonia and elevated plasma CRP increased the association with TL gain but reduced the association with KHL gain during OTC. There is need to strengthen prevention, early diagnosis, and treatment of infections plus other conditions associated with impaired gut function in children with SAM, as this may be beneficial in recovery of linear growth in these children. In order to optimize recovery in linear growth among children treated for SAM, further research is needed to understand the regulation of ponderal compared with linear growth and to determine factors modifying linear growth of the different body parts.

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