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NUTRITIONAL SUPPLEMENTATION AND MUSCLE MASS PRESERVATION IN ADULTS DURING BED REST: A SYSTEMATIC REVIEW TO INFORM CLINICAL PRACTICE

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Abstract: *Background:* Nutritional intervention is assumed to protect muscle mass in patients at bed rest. This review found no high quality studies performed in the clinical setting, with evidence limited to the effect of nutritional supplementation on lean muscle mass and functional outcomes. *Objectives:* This systematic review investigates whether nutritional intervention, in the absence of other countermeasures, is effective in preserving muscle mass during periods of bed rest. It considers relevant studies within a clinical context and critiques the nutritional methodologies used. *Evidence review:* Studies were identified by electronically searching MEDLINE, CINAHL, EMBASE and PubMed from the earliest available to September 2012, as well as a citation review of relevant papers. Included studies had at least one group receiving oral nutritional supplementation or a higher protein diet during bed rest in comparison to a control group not receiving nutrition intervention. Nutritional methodologies were investigated using a standardised protocol, and a meta-analysis was conducted. *Findings:* The initial search yielded 310 studies with six of these meeting inclusion criteria for the review. Methodological issues included an absence of detailed recruitment strategies, participants who were mostly young healthy males, and space flight as the primary study context. This limited the ability to extrapolate results to the clinical setting of older hospitalised patients at bed rest. A meta-analysis indicated that nutritional supplementation did not improve lean leg mass during bed rest. *Conclusion:* High level evidence to support the use of nutritional supplementation in protecting muscle mass during bed rest is lacking, especially in elderly patients under clinical situations. Translational trials are needed to direct clinical practice for healthcare providers.

Key words: Oral nutritional supplementation, bed rest, muscle mass, protein, clinical practice.

Introduction

Hospitalisation often requires a period of bed rest, whether as a prescribed treatment for a medical condition or due to an inability to mobilise (1). Prolonged bed rest reduces whole body protein synthesis rate resulting in a loss of lean tissue, particularly in the lower limbs (2, 3). The elderly are especially vulnerable to accelerated muscle loss in hospital compared to their younger counterparts (4), which may be compounded by pre-existing sarcopenia. It has been estimated that each day an older person spends in a hospital bed results in a five percent decrease in muscle mass, with the reconditioning time taking longer than the deconditioning time (5). Given the consequences of bed rest on lean tissue, strength and function, and the even greater impact on the elderly, innovative models of care are required to mitigate these effects.

Illnesses such as malnutrition can also impact on lean body tissue as the rate of muscle loss is accelerated even more when a hospitalised patient is malnourished (6). Malnutrition in the hospital setting has been well documented internationally, with up to 50% of hospitalised patients classified as malnourished (7-9). Negative outcomes for these patients not only include increased muscle loss but also longer length of stay (10-12). Chronic protein losses are associated with progressively decreased immune competence, poorer wound healing, and increased susceptibility to disease (13). Most often it is the frail and medically compromised person that is placed in bed for a long time thus, coupled with malnutrition, may lead to an increase in health resources in this group of patients.

Exercise approaches to limit muscle atrophy due to disuse have been extensively researched, particularly in the younger population (14-16). Low intensity exercise such as weight bearing or walking may provide some benefit (17, 18), with neuromuscular electrical stimulation

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a potential alternative in those where resistance training or ambulation is not possible (19). Furthermore, a recent meta-analytic review examining the effect of dietary protein supplementation on the adaptive response of skeletal muscle to prolonged resistance-type exercise training proposed benefits of protein supplementation to augment muscle mass (20).

Whilst there are proposed benefits for nutritional supplementation alone to be effective in maintaining muscle mass and function during bed rest, such as with the use of protein or amino acids, the evidence is conflicting. Some studies have reported a benefit in attenuating muscle mass and function (21-23), others have not confirmed such benefits (24-26), although different study designs may have also attributed to the discrepancy of results. Several authors (13, 27, 28) have reviewed the effect of nutritional supplementation on muscle mass and bed rest, with none of these reporting the results in a systematic manner and with limited consideration of bed rest in the clinical setting.

Whilst it seems that aging per se appears to facilitate inactivity-mediated muscle loss, it appears that even a brief, clinically mandated period of bed rest could initiate a serious decline in muscle strength and functional capacity (28). Without robust countermeasures (nutritional, exercise, or pharmacological), lean tissue loss seems largely inevitable during prolonged be rest, requiring innovative strategies and therapies to preserve muscle mass and function. Physical interventions such as exercise provide a promising anabolic stimulus, but exercise may not be a feasible countermeasure in all situations, particularly when bed rest is the result of injury or trauma (29). On the basis of the available literature, there is uncertainty whether nutritional supplementation has any benefits on the gain of muscle mass and/or strength during bed rest. This systematic review aimed to investigate whether the effect of nutrition intervention, in the absence of other countermeasures, is effective in preserving muscle mass during bed rest. Compared with previous reviews, this study focused on assessing the nutritional methodologies used and the application of results to the clinical setting.

Methods

This review was conducted with guidance from with the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) statement (30).

A protocol for this review was registered with PROSPERO (http://www.crd.york.ac.uk/PROSPERO), registration number CRD42012002949 in September 2012.

Search strategy

A search strategy was developed to identify appropriate studies for review, supported by a medical librarian. The electronic databases MEDLINE, CINAHL, EMBASE and PubMed were searched from the earliest available to September 2012. Search terms included were bed rest, bedrest, immobile, immobility, reduced activity, reduced mobility, inactivity, dietary protein, dietary fat, dietary carbohydrate, dietary nitrogen, dietary amino acids, nutrition supplements, muscle mass, muscle strength, muscle function and skeletal muscle. In addition, reference lists of selected studies were manually searched for additional papers that met the inclusion criteria.

Study selection

Published English language studies that directly compared the effects of oral nutritional supplementation on muscle mass during bed rest or prolonged inactivity as a primary outcome were included for consideration. No universal definition of bed rest, prolonged inactivity and reduced activity was found; therefore studies with these terms were included for analysis. Only human studies published in English-language journals were included. Studies from scientific conferences, commentaries, reviews, or duplicate publications from the same study were not included. All included research articles contained a nutritional intervention with at least one subject group receiving a nutritional/protein supplement or a modified higher protein diet during bed rest. Each study additionally needed to contain a control group that did not receive a nutritional supplement or received a lower protein/energy diet during bed rest.

Eligibility assessment was performed independently by both authors. Study titles and abstracts initially were screened and inclusion/exclusion criteria applied, with inter-reviewer disagreements resolved by consensus (Table 1). Potential abstracts were then retrieved in full text for evaluation against inclusion/exclusion criteria. Both reviewers agreed on the final decision of studies to be included for review.

Data extraction and quality assessment

For included studies, data were extracted using a customised form (Table 2). Data extraction included reference details, quality rating, study design, population characteristics and participant numbers, duration of bed rest, description of intervention and control and results. One review author extracted the data from included studies and the second author checked the extracted data. Disagreements were resolved by discussion between the two review authors until consensus was reached.

Unlike previous reviews, the current review specifically investigated the nutritional methodologies of studies to establish their appropriateness and hence application to the clinical setting. The Academy of

Table 1
PICO model of inclusion and exclusion criteria for literature search

Model category	Inclusion criteria	Exclusion criteria
Population	Human, adults, immobility or bed rest	Animal, children and adolescents, not immobility or bed rest
Intervention	Trials with subjects receiving oral nutritional supplements in the form of protein/amino acids/energy/fat/carbohydrate, or combination	No nutritional supplementation intervention
Comparison	Receiving no treatment; control group	Lack of comparison/control
Outcomes	Reported muscle mass, strength or function	Muscle mass, strength or function not reported

Nutrition and Dietetics Quality Criteria Checklist for Primary Research (31) was chosen for quality assessment as this tool critiques dietary methods unlike the majority of other quality assessment tools. Each study was evaluated using the four relevance questions that addressed applicability to practice and ten validity questions that addressed scientific soundness. Scoring was applied in accordance with the checklist rating to determine an overall quality rating of plus/positive (+), neutral (Ø) or minus/negative (-). The studies were appraised independently by the authors, with consensus resolved by discussion.

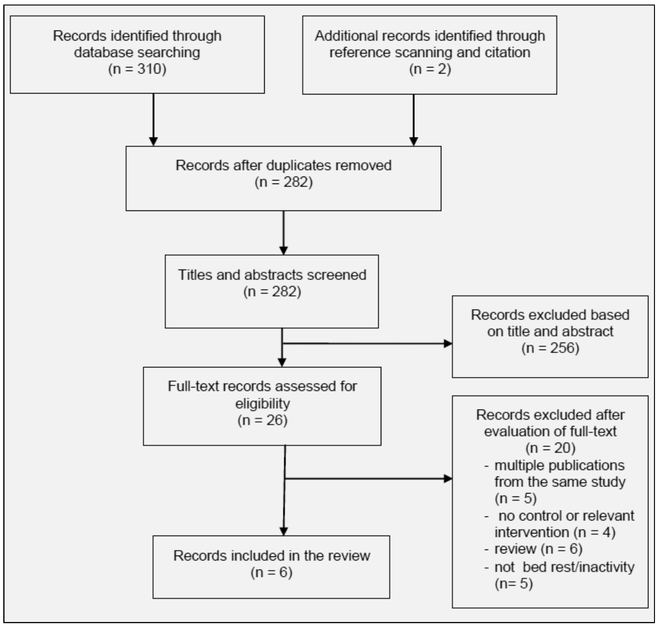
Data analysis

A meta-analysis was conducted examining the effects of nutritional supplementation on muscle mass on control and treatment groups. To account for measurement variability between studies, the meta-analysis was performed with a random-effects model. A forest plot was generated using RevMan (Review Manager version 5.2), provided data were clinically homogenous, with similar populations, interventions and outcomes (32, 33). RevMan data entry conversions were consistent with the Cochrane Handbook (33). Standardised mean differences were calculated for the outcomes when standardised mean errors were reported. Statistical heterogeneity between included studies was assessed using the I^2 index, with values of more than 50% representing substantial levels of heterogeneity (34).

Results

A total of 310 studies were identified by the search strategy and after adjusting for duplicates 282 remained (Figure 1). Of these, 256 studies were discarded after reviewing the abstracts because they clearly did not meet the inclusion criteria. An additional two publications were included following screening of reference lists of included studies. The full text of the remaining 26 papers was examined in more detail, with a further 20 studies not meeting the inclusion criteria described. In some instances multiple publications had arisen from the same study. Of these, the study reporting results that most closely approximated with the aim of this review was included, others were excluded. Of the remaining papers, four had no control or relevant intervention, six were reviews and five were not bed rest studies. Six studies met the inclusion criteria and were included for review. The publication dates ranged from 1990 to 2010. Key features of the six studies are summarised in Table 2.

Figure 1
Flow diagram of search process for systematic review of nutritional supplementation and muscle mass preservation during bed rest



Study characteristics

Of the six included studies, five were conducted in the USA (21-25) and one in France recruiting subjects from within the European Union (26), with sample sizes ranging from 12 to 21 subjects. The duration of the interventions were between 6 and 60 days of bed rest. The studies combined involved 87 healthy, community dwelling volunteers. Three studies were conducted with

Table 2
Summary of included studies

Author & location	Quality rating (31)	Study design and population characteristics	Duration of bed rest (d)	Experimental group	Control group	Results	Comments
Stein et al. 1999 (25) USA	ø	Randomised trial. N = 14 Mean age 31 yr (control) Mean age 29.9 yr (exp) Healthy men and women	6	BCAA Protein intake approx. 1.06g/kg/day*	NEAA Protein intake approx. 1.13g/kg/day*	Greater nitrogen retention in experimental group. No functional outcomes reported.	Slightly higher amount of nitrogen consumed in the BCAA group.
Stuart et al. 1990 (21) USA	ø	Non-randomised, experimental trial. N = 12 Age range 18-31years (control and experimental groups not distinguished for age) Healthy men	7	Diet containing 1.0g/kg/d protein	Diet containing 0.6g/kg/d protein	Improved nitrogen balance in experimental group. Whole body protein synthesis decreased in control group, but maintained in experimental group. No functional outcomes reported.	Both diets were isocaloric
Paddon-Jones et al. 2004 (22) USA	ø	Randomised trial. N = 13 Mean age 38 yr (control) Mean age 36 yr (exp) Healthy men	28	EAA and CHO supplementation Protein intake = 1.5g/kg/d	Standard meal with no supplementation Protein intake = 0.8g/kg/d	Maintenance of lean leg mass in experimental group. Loss of leg extension strength in both groups, significantly more in the control group.	Energy intake was also increased with protein supplementation so it cannot be determined whether the benefits were due to the amino acids, the extra energy, or the extra energy and amino acids together.
Ferrando et al. 2010 (23) USA	ø	Non-randomised, experimental trial. N = 21 Mean age 68 yr (control) Mean age 71 yr (exp) Healthy men and women	10	EAA Protein intake = 1.4g/kg/d	Baseline diet with no additional EAA Protein intake = 0.8g/kg/d	Decrease in total and lean leg mass in both groups. Maintenance of muscle strength in experimental group. Floor transfer time was impaired in control group and maintained in experimental group.	
Stein et al. 2003 (24) USA	ø	Randomised trial. N = 12 but unclear Mean age 35.5 yr (control) Mean age 38 yr (exp) Healthy men	14	BCAA supplementation Protein intake = 1.2g/kg/d	Equimolar mixture of NEAA Protein intake = 1.0g/kg/d	Increased nitrogen balance in experimental group. No effect of BCAA on protein synthesis or protein breakdown. No functional outcomes reported.	
Trappe et al. 2007 (26) France	ø	Non-randomised, experimental trial. N = 16 Mean age 34 yr (control) Mean age 29 yr (exp) Healthy women	60	Protein with additional leucine Protein intake = 1.6g/kg/d	Baseline diet without additional EAA Protein intake = 1.0g/kg/d	Greater loss of thigh muscle volume in experimental group. Overall muscle strength decreased in control and experimental groups.	Exercise was an additional study arm.

EAA, essential amino acids; LBM, lean body mass; CHO, carbohydrate; BCAA, branched chain amino acids; NEAA, non-essential amino acids; *Extrapolated from nitrogen balance data.

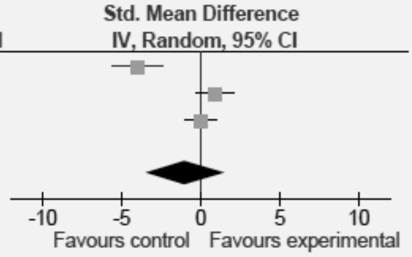
Figure 2

SMD (95% CI) for the effect of nutritional supplementation on leg lean mass by pooling data from 3 trials (n=49)

Study or Subgroup	Experimental Mean	Experimental SD	Experimental Total	Control Mean	Control SD	Control Total	Weight	Std. Mean Difference IV, Random, 95% CI
Ferrando 2010	12.5	0.23	11	13.6	0.3	9	31.5%	-4.00 [-5.64, -2.36]
Paddon-Jones 2004	0.2	0.79	7	-0.4	0.25	6	33.8%	0.92 [-0.25, 2.09]
Trappe 2007	0.6	0.11	8	0.6	0.09	8	34.6%	0.00 [-0.98, 0.98]
Total (95% CI)			26			23	100.0%	-0.95 [-3.42, 1.52]

Heterogeneity: Tau² = 4.33; Chi² = 24.03, df = 2 (P < 0.00001); I² = 92%

Test for overall effect: Z = 0.75 (P = 0.45)



SMD, standard mean difference

only male subjects (21, 22, 24), one study was conducted with only female subjects (26), and two studies were conducted using both male and female subjects (23, 25). Five studies were conducted in younger (<50 years) subjects (21, 22, 24-26) and one study in older (>60 years) subjects (23). Three studies (22, 24, 25) reported that subjects were randomised (although randomisation techniques were not described). For the other three studies included for review (21, 23, 26), randomisation was not reported therefore it was assumed that these studies were non-randomised, experimental trials.

The included studies had differing protocols and intervention models however sufficient commonality enabled comparison of results to be made. One study had an exercise component (26), some compared nutritional supplementation against the baseline diet, and others compared essential amino acids against non-essential amino acids. The nutritional feature of all studies was either protein or amino acid supplementation and only one used additional carbohydrate (22). Four of the studies reported an effect of nutritional supplementation between treatment and control groups (21-23, 25) and two did not (24, 26) (Table 2).

Stein et al. (25) investigated the effects of increased amounts of branched chain amino acids (BCAA) in the diet during six days of bed rest. It was observed that BCAA supplementation attenuated the nitrogen loss during short-term bed rest. Stuart et al. (21) focused on the effects of increasing dietary protein isocalorically from 0.6 to 1.0 g/kg/d on whole body protein metabolism, concluding that the higher dietary protein intake maintained whole body protein synthesis and improved nitrogen balance.

Two studies investigated the effect of nutritional supplementation on lean mass. Paddon-Jones et al. (22) tested combined essential amino acids (EAA) and carbohydrate supplementation against standard meals containing intact proteins. Supplementation increased the protein intake from 0.8 to 1.5 g/kg/d.

The results showed that supplementation of EAA and carbohydrate maintained lean leg mass and mitigated loss in strength. However, owing to the extra energy that was consumed with protein supplementation, it was difficult to separate the effects of amino acids, the extra energy, or the extra energy and amino acids on muscle protein mass and strength. Ferrando et al. (23) investigated an older study group and showed that EAA supplementation maintained muscle strength during 10 days of bed rest. However, total lean and leg lean mass showed no effect from EAA supplementation. Total protein intake was increased from 0.8 to 1.4 g/kg/d with supplementation.

Two further studies showed no effect of nutritional supplementation on muscle mass or on protein metabolism. Stein et al. (24) investigated the effects of BCAA supplementation compared to an equimolar mixture of non-essential amino acids, providing an increase of 1.0 to 1.2 g/kg/d of total protein. There was no effect of BCAA supplementation on either whole body or muscle protein synthesis or protein breakdown during 14 days of bed rest, although nitrogen retention was greater with BCAA supplementation. Trappe et al. (26) studied the effects of additional EAA on lower limb muscle volume and strength, as part of the multi-national 2005 Women International Space Simulation for Exploration (WISE) bed rest study. Protein intake was increased from 1.0 to 1.6 g/kg/d, with the nutrition group receiving essential leucine. The authors noted that leucine has a strong stimulatory ability and anti-catabolic effects. Results showed no effect for thigh or calf muscle volume and strength, with a greater loss of muscle volume of the thigh in the nutrition group.

The six studies reviewed were assessed for research design using the Academy of Nutrition and Dietetics Quality Criteria Checklist for Primary Research (31) but none could fulfil the validity criteria. Both authors had 100% agreement on all aspects of the checklist for each study and all studies were agreed to be neutral, indicating that the articles were neither exceptionally strong nor exceptionally weak for the research and dietary methods used. All studies scored positively for the four relevance questions in the checklist, indicating they were applicable to practice. However, the validity questions that addressed scientific soundness of the studies led to a neutral conclusion, with unclear results recorded primarily in relation to selection of subjects, methods of assigning subjects to study groups, method of handling withdrawals, in addition to blinding of subjects and practitioners.

Meta-analysis

Nutritional supplementation did not have an effect on lean leg mass during bed rest when compared to no intervention in three trials (n=49), (SMD=-0.95; 95% CI, -3.42 to -1.52; I^2=92%) (Figure 2). There was a very large degree of data heterogeneity.

Discussion

The results of this systematic review provide evidence from six interventional studies that nutritional supplementation does not maintain lean leg mass nor significantly improves functional outcomes. The review has found that most of the studies examining the effect of protein supplementation on bed rest have been in the interest of space-flight using ground based models. Little published research has focused on countermeasures towards bed rest-induced muscle loss during periods of hospitalisation. The results from space-flight models appear to have been extrapolated to clinical settings but do not take into account serious illness or the effects of aging. No fully effective measures for preventing muscle loss associated with space-flight have been found. Additionally, no studies have directly compared younger and older adults during bed rest, with only one study examining bed rest in the elderly (23).

Overall the published studies in this review indicate some ambiguity in relation to amino acid/protein supplementation protecting against muscle atrophy during bed rest. Some researchers (21, 24, 25) reported nitrogen balance, rather than leg or muscle mass, as a research outcome or endpoint. The translation of these data to their effect on muscle mass or functional outcomes cannot be assumed, minimising extrapolation to the clinical setting. The only research conducted in the elderly concluded that "additional protein alone is not capable of reducing the loss of lean mass during inactivity in the elderly" (p.21) (23). However, positive functional outcomes from supplementation were noted. This is inconsistent with the review by Wolfe et al. (35), who described that the anticipated acute stimulating effect of additional protein should increase lean body mass, strength and function. During periods of bed rest, it appears that exercise is needed as a co-treatment to support the maintenance of muscle mass.

Functional outcomes were considered by three of the included studies (22, 23, 26). Both muscle strength and floor transfer time were more positive in the elderly intervention group of Ferrando et al. (23). Of the studies undertaken to support space research, Trappe et al. (26) found no significant functional improvements in the intervention group and Paddon-Jones et al. (22) reported loss of leg extension strength in both groups (although significantly more in the control group). No conclusive outcomes can be drawn from the variable and limited data presented.

This review found varying research protocols, often determined by the needs of the respective space program. Some had an activity component, some compared supplementation against a baseline diet and others compared essential amino acids against non-essential amino acids. The meta-analysis in Figure 2 highlights this through large effect sizes, with the effect of protein supplementation on leg muscle mass favouring the control group.

The inconsistency in defining baseline protein requirements for control and treatment groups further limits the interpretation of study results. Three of the six studies applied baseline protein intake at the current RDA (0.8 g/kg/d) (36) or provided additional energy to bring the subject closer to their habitual pre-bed rest intakes. Recent studies have re-evaluated human protein requirements at a 41% higher level than current recommendations (37, 38). Perhaps current recommendations of 0.8g/kg/d protein used for some bed rest studies is inadequate, with some authors suggesting that the positive effects of amino acid supplementation observed on protein metabolism simply reflect the benefits of providing an adequate protein intake, rather than a protective effect against bed rest induced disease (13).

The recent review by Wall and van Loon (p.204) (27) "speculated that supplementation with 30g of high-quality dietary protein (containing approximately 15g of essential amino acids and approximately 3g of leucine) three to five times daily should be effective in attenuating muscle mass during a period of disuse". The meta-analysis and investigation of nutritional methodologies in the present review challenges these findings. In the absence of exercise, maintenance of leg mass is unlikely through protein supplementation alone.

An additional recent small randomised control trial by Deutz et al. (39) in healthy adults reported positive outcomes of lean body mass, but not functional outcomes, of a calcium salt during bed rest, posing a further opportunity for bed rest research within the clinical setting.

The current review considered the evidence for hospitalised patients undergoing a period of clinically induced bed rest. The primary research reviewed had methodological and setting limitations so results need to be interpreted carefully. Extrapolation of these data into the clinical setting is limited due to the disease effects of sarcopenia and malnutrition experienced in the usual hospital bed rest population.

The absence of translational research examining the effect of protein and/or amino acid supplementation on preserving muscle mass is a clear practice gap. Clinicians are reliant on interpreting the body of malnutrition research where multi-nutrient oral nutritional supplements (high energy and/or protein) and other interventions have preventative and treatment effects (40-44). It is difficult to draw reliable clinical conclusions from the present review where the majority of studies have been in healthy young males. Randomised controlled trials or other interventional studies in the clinical setting to support or disregard the results of bed rest in space-flight conditions are needed. Without these, patients will continue to receive protein supplements during bed rest in the hope of preserving muscle mass, at much expense to health services.

Warranting further exploration too is whether the use of essential amino acids, especially in the elderly, may be of benefit due to preventing early satiety that traditional oral nutritional supplements can have. It is known that energy intake from high energy-high protein supplements may only substitute energy that would otherwise be consumed from food sources. Again, these data are absent for the clinical setting of patients undergoing bed rest.

In today's resource-constrained environment, no longer can nutrition intervention be administered based on robust evidence alone (although this was not conclusively demonstrated in this review), but needs to consider endpoints such as cost effectiveness as well. Without undeniable evidence that nutritional intervention is cost effective and improves patients' quality of life, resistance may be encountered to implementing nutritional therapy into routine care (27). Thus, high quality studies that ascertain whether protein supplementation can preserve muscle mass in patients at bed rest are needed. These studies would need to separate the effects of immobilisation from the metabolic effects of cachexia – or accept protein supplementation may benefit both of these where they happen simultaneously.

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