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LEUCINE SUPPLEMENTATION IN THE MANAGEMENT OF PROTEIN ENERGY MALNUTRITION: A REVIEW

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ABSTRACT

***Background*: Wasting accounts for 4.7% of all deaths of children under five years of age globally. Currently there is no standard for treatment of moderate wasting in children resulting in high variability of treatment methods and low predictability of recovery outcomes. Leucine, a branched chain amino acid,has recently received significant attention as a therapeutic agent for the treatment of numerous muscle wasting conditions. This is attributed to its ability to accelerate protein synthesis and reduces protein breakdown in the muscles.**

***Objective:* To establish if leucine could be used as a therapeutic agent in the treatment of protein energy malnutrition.**

***Study selection:* Based on defined key words a search was carried out on Pubmed to retrieve all publications on leucine supplementation and muscle protein synthesis. Only studies that met the search criteria were retrieved and the required data obtained.**

***Data synthesis:* Eightunique studies obtained from 8 articles that met the study criteria were included. The publications were analysed to establish whether leucine supplementation had any effect on muscle protein synthesis and protein break down. Dosage levels used in the studies if available were also duly noted.**

***Results*: The articles reviewed indicated that leucine supplementation either led to enhanced protein synthesis or reduced muscle mass loss in both healthy participants and participants with wasting conditions**

***Conclusion:* Leucine supplementation is a safe and effective way to enhance muscle protein synthesis and reduce loss of lean mass in catabolic conditions. Given the low effectiveness of current therapeutic feeds used in the management of moderate malnutrition, leucine supplementation should be given significant consideration as a potential strategy for treating the condition.**

INTRODUCTION

Protein energy malnutrition represents a depletion of the body's lean tissue caused by starvation and if it's not adequately managed it leads to wasting (1). Wasting occurs when the weight for height z-score of a child drops below minus two standard deviation from the median of the reference population. Wasting is classified as either; moderate, when the weight for height z-score is greater than or equal to minus 3 but less than minus 2, or severe where the z-score is less than minus 3 (1).

Wasting accounts for 4.7% of all deaths of children under 5 years of age globally(2).This is because wasted children are 11 times more likely to die than healthy children(2). Globally it is estimated that any given point in time in the world, 52 million children under the age of 5 years are wasted with 17 million of those severely wasted. The World Health Assembly wasting target is set at reducing and maintaining levels of childhood wasting to below 5 percent(3). In Kenya, 4 percent of children under the age of five years are wasted and 1 percent are severely wasted. Wasting levels are highest among children in the age groups 6-8 months and 9-11 months (each 7 percent). In this period, children are being introduced to complementary feeds and are more susceptible to illnesses. Wasting in children is highest among households in the lowest wealth quintile. Wasting in Kenya is highest in the counties towards the north of the region including: Mandera, Marsabit, West Pokot, Garissa, Wajir, Turkana and Samburu. More than 11 percent of children in these counties are wasted with Turkana having the highest number at 23 percent(4).

The standard of care in severe wasting requires the use of measures to correct fluid and electrolyte imbalances, and replenish calories, proteins and micronutrients(5). Treatment starts with modest amounts of calories and proteins based on a person's actual weight to avoid complications. Simultaneously, minerals and vitamins are administered. However administering water and sodium with carbohydrates can overload a heart that has already been weakened due to malnutrition resulting in congestive failure(6).

In the case of moderate wasting there is no definitive consensus on the most effective way to treat it. There are different approaches used to address moderate malnutrition with prepared foods that include; providing lipid-based nutrient supplements or blended foods, either a full daily dose or in a low dose as a complement to the usual diet(7). A study done to evaluate the effectiveness and safety of different types of specially formulated foods for children with moderate acute malnutrition concluded that both lipid-based nutrient supplements and blended foods have limited effectiveness in treating children with moderate acute malnutrition. In addition, lipid-based nutrient supplements do not reduce mortality, the risk of progression to severe acute malnutrition and they also induced more vomiting(7). These poor outcomes attributed to the high variability and low effectiveness of current treatment methods of moderate malnutrition justifies the need to study other alternatives including leucine as an effective way to manage the condition.

Leucine, a branched chain amino acid, has recently received significant attention as a therapeutic agent for the treatment of several muscle wasting conditions.Since lean tissues account for the largest body compartment, their rate of loss is the most significant determinant of total body weight in most cases of protein energy malnutrition(6).The objective of this study was to therefore establish if leucine could be used as a therapeutic agent in the treatment of protein energy malnutrition.

MATERIALS AND METHODS

Published material which covered leucine and protein synthesis were searched on Pubmed and gathered. Articles were reviewed to establish whether there is any significant association between leucine supplementation and muscle protein synthesis. Literature search was done using the following keywords; 'leucine and protein synthesis', 'leucine and muscle wasting' and 'leucine supplementation' *Study Selection:* From the above search criteria there were 47 articles that were retrieved. Articles were rejected if they did not discuss leucine in relation to muscle protein synthesis, if the statistical analysis used was not suitable, if the study was not done on humans or rodents (or their cultured tissues) and if the article was a review of other publications. Out of the 47 articles retrieved 39 were excluded because they did not meet the aforementioned requirements leaving 8 publications to be reviewed. The publications reported on 8 studies from 4 countries.

RESULTS

Table 1 shows key information obtained from the studies that were reviewed. This included; the year of publication, the country, the authors, the study group or materials used, the study design and the results. From the studies reviewed, 3 were conducted on rats with varying characteristics, 1 was conducted on adults, 1 on premature infants, 1 on children with cystic fibrosis and the rest on cultured cells. It was noted that leucine supplementation either led to enhanced protein synthesis or reduced muscle mass loss in all the studies. Of significant interest was that leucine supplementation in children with cystic fibrosis who typically have poor weight gain and growth (synonymous with protein energy malnutrition) resulted in reduced protein breakdown.

Table 1
Some of studies done associating leucine supplementation and protein synthesis

Serial Number	Year	Country	Author	Study group/ study materials	Study design	Conclusion	Most effective dosage
1	2014	Switzerland	Churchward -venne T.A et al	Young male strength athletes	Double-blind randomized trial	Leucine supplementation enhanced-myofibrilla protein synthesis	5 gms
2	2012	Netherlands	Haegens A. et al	Cultured C2C12 skeletal muscle cells	Experimental lab-based	Leucine supplementation increased myofibrillar protein accretion	500 μM
3	2011	Netherlands	Peters S.J., et al	Cancer cachectic mice	Randomized control trial	Leucine supplementation reduces muscle wasting in cancer cachectic mice	Not specified
4	2010	Brazil	Baptista I.L. et al	Immobilized hind limbs	Experimental lab-based	Leucine supplementation attenuated muscle mass loss caused by immobilization	Not specified
5	2006	Netherlands	Van der Akker C.H.P et al	Premature infants control trial	Randomized supplementation	Leucine2.4 g/kg/day resulted in anabolic state due to increased protein synthesis	
6	2005	USA	Crozier S.J. et al	Lab rats	Randomized control trial	Leucine supplementation stimulated muscle protein synthesis	1.35 g/kg body weight
7	2000	USA	Anthony J.C	Food-deprived Lab rats	Randomized control trial	Leucine supplementation stimulates protein synthesis in the muscles of food-deprived rats	270mg
8	1999	USA	Kien L.C. et al	Children with cystic	Randomized fibrosis	Leucine uptake control trial resulted in reduced protein breakdown.	Not specified

DISCUSSION

Muscle protein synthesis is triggered by continuous hydrolysis of all intracellular and extracellular proteins causing them to be broken-down to their constituent amino acids and replaced by new synthesis(8). However when the process of protein breakdown is accelerated due to several catabolic conditions including protein energy malnutrition it results in muscle mass loss(8). During states of insufficient caloric intake, the breakdown of cell proteins, particularly in skeletal muscle, increases to provide the body with amino acids essential for gluconeogenesis, energy production and new protein synthesis.This acceleration of protein breakdown resulting in muscle wasting mainly occurs due to activation of the ubiquitin (Ub) proteasome pathway(8).

Leucine supplementation has been shown to be an effective strategy in increasing muscle protein synthesis in humans and rodents(9) even in states of muscle wasting. Leucine supplementation activates messenger ribonucleic acid translational machinery through mammalian target of rapamycin in an insulin dependent or independent process. The signalling of mammalian target of rapamycin is activated by insulin-like growth factor-I and insulin. These factors activate P13-k pathway and Akt resulting in mammalian target of rapamycin phosphorylation(10). The phosphorylation of mammalian target of rapamycin, resulting in up-regulation of protein translation through the phosphorylation of the

eukaryotic initiation factor 4E binding protein 1 (4E-BP1) and the ribosomal protein S6 kinase (S6K) leading to cell growth and proliferation (9, 11, 12). Unlike insulin and insulin-like growth factor-1, leucine has a direct effect at an intracellular locus modulating protein signalling pathways. Further, leucine does not appear to need the mediation of a cell membrane receptor(13), acting efficiently in the protein synthesis.

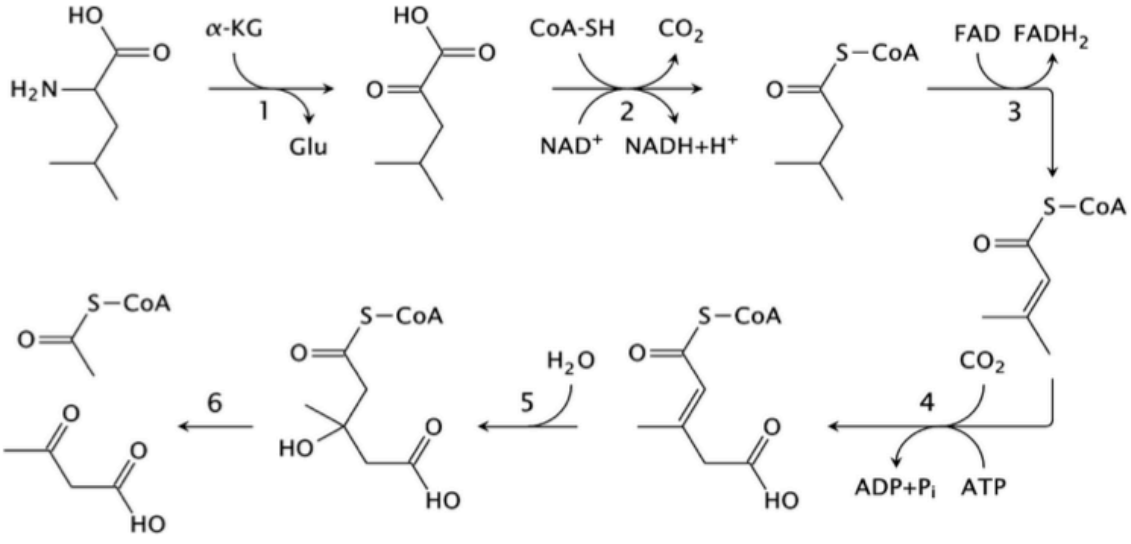
As seen in Figure 2, once in the body, leucine undergoes degradation mainly in the skeletal muscle where it istransaminated by branched chain amino acid transaminase. This yields α-ketoisocaproate which.is then decarboxylated and dehydrogenased by branched chain α-keto acid dehydrogenase. The resulting metabolite, isovaleryl-CoA undergoes a dehydrogenation reaction by isovaleryl-CoA dehydrogenase yielding isopentenyl-CoA. Biotin-dependent carboxylation yields methylglutaconyl-CoA. Addition of water by methylglutaconyl-CoA hydratase yields HMG-CoA. HMG-CoA lyase then splits HMG-CoA to acetyl-CoA and acetoacetate(14).

When considering the safe intake level of leucine, 500 mg/kg/dayis proposed as the upper limit (15). This is because, with increasing intake amounts of leucine, a clear dose response in leucine oxidative capacity, measured as $F13CO_2$ from the oxidation of l-[1-13C]leucine, is observed. Significant increases in blood ammonia concentrations are observed at leucine intakes greater than 500 mg/kg-/day. At a leucine intake of 250 mg/kg-/day, the mean fed-state ammonia concentrations are within normal limits, but at a leucine intake of 500 mg/kg-/day, the mean ammonia concentration is beyond the normal limits(16). Therefore when chronic ingestion studies are being developed, leucine intake levels should range between 250–300 mg/kg-/day(17).

In addition, one must also put into consideration the protein content of the diet when considering the safe intake level of leucine(18). The relative amount of branched-chain amino acids in the diet is the main determinant of the adverse effects of excessive leucine(18, 19). Excess dietary leucine induces a secondary drop in the reserves of the structurally analogous antagonistsvaline and isoleucine and the addition of one or preferably both of these branched-chain amino acids has been shown to reduce these effects of leucine(18). While there have been no adequate studies on the best ratio of Leucine to isoleucine to valine in leucine supplements most commercially available products have these branched-chain amino acids in a ratio of 2:1:1 per serving size.

In conclusion leucine supplementation is a safe and effective way to enhance muscle protein synthesis and reduce loss of lean mass. Given the low efficacy of current therapeutic feeds in the management of moderate malnutrition, leucine supplementation should be given significant consideration as a potential strategy for improving the weight for height z-score of children with moderate malnutrition.

Figure 1
The Pathway of Leucine Degradation



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