NUTRITIONAL THERAPY & METABOLISM

Rinpe
Official Journal
of the Italian Society of Parenteral and Enteral Nutrition
(SINPE) A Member of FeSIN

Effects of an amino acid formula administered orally to malnourished HIV-positive patients: short-term results

PAOLA MANFRIN, CONSUELO VECCHIO, DAVIDE MINISCI, FULVIO MUZIO

Wichtig Editore
Milano - Birmingham, AL. - Osaka

Reprinted from
Vol. 31, No. 1, pp. 40-44
January-March

Nutritional Therapy & Metabolism 2013; 31 (1): 40-44 DOI: 10.5301/NTM.2012.9926

ORIGINAL ARTICLE

Effects of an amino acid formula administered orally to malnourished HIV-positive patients: short-term results

Paola Manfrin, Consuelo Vecchio, Davide Minisci, Fulvio Muzio

Clinical Nutrition Unit "Luigi Sacco" University Hospital, Milan - Italy

ABSTRACT

Introduction: *Since the recognition of the acquired immune deficiency syndrome, malnutrition has been considered one of the factors that characterize the disease. The purpose of this study was to evaluate the effect of oral supplementation with an amino acid formula on the nutritional status of malnourished HIV-infected patients.*

Patients and Methods: *The study was carried out in 10 seropositive malnourished patients. All subjects were given a personalized calorie-balanced diet supplemented with Aminotrofic©. Blood tests and body composition assessment by DEXA total-body scan were performed at T0 and T1 (3 months).*

Results: *After 3 months of treatment a significant increase in total protein, albumin and insulin was observed. The significant increase in insulin levels can be ascribed to an increase of the anabolic stimulus.*

Conclusions: *The data from this study suggest that the combination of a balanced diet with an amino acid formula may have a positive role in promoting and/or improving skeletal muscle protein deposits.*

KEY WORDS: *Malnutrition, HIV infection, Amino acids, DEXA scan, Dietary supplements*

Received: January 28, 2011; Accepted: April 11, 2011

INTRODUCTION

Malnutrition is an important predictor of morbidity and mortality whose origin may be ascribed to several factors including reduction of food intake, malabsorption, and metabolic impairment. Since the 1980s, when the acquired immunodeficiency syndrome was first recognized, malnutrition has been considered one of the factors that characterize the disease (1-3). Malnutrition may in fact adversely affect an immune system already compromised by underlying diseases and it is documented that malnourished people receiving antiretroviral treatment have a 6-fold higher probability of death than those adequately fed (4).

Cytokines, particularly tumor necrosis factor-alpha (TNF-α), are known to be involved in the catabolism of skeletal muscle in several diseases such as HIV infection (5), cancer (6), and chronic obstructive pulmonary disease (7). TNF-α can inhibit the secretion of testosterone, which is known to act as a regulator of muscle mass. TNF-α can also influence tissue sensitivity to hormone signals and directly stimulate protein catabolism (8, 9). In HIV-infected patients serum levels of soluble TNF are higher than in healthy controls (10) and circulating TNF-α is inversely correlated with changes in lean body mass (11).

The availability of amino acids is a key factor in maintaining the general and cellular metabolism and protein synthesis of mammalian muscle. Some data suggest that oral supplementation of exogenous amino acids, counteracting muscle wasting and reduction of cellular energy, can improve cardiac function and quality of life (12, 13).

The purpose of this study was to evaluate the effect of oral supplementation with an amino acid formula on the nutritional status of malnourished HIV patients.

Wichtig Editore - © 2012 SINPE-GASAPE - ISSN 1828-6232

SUBJECTS AND METHODS

Participants

The present study involved 10 HIV-seropositive individuals (5 women and 5 men) aged between 36 and 60 years, with a body mass index (BMI) between 14.8 and 20.3 kg/m^2. Enrolment took place at the Outpatient Infectious Diseases Clinic of the University Hospital L. Sacco in Milan.
The inclusion criteria were HIV seropositivity with a diagnosis of malnutrition based on a BMI <18.5 and/or weight loss >5% in the last 3 months, or >10% in the last 6 months. The exclusion criteria were HIV seropositivity with a good nutritional status; HIV seropositivity with cachexia and artificial feeding; HIV seropositivity and acute comorbidities.

Study design

All 10 subjects were given a custom balanced diet (35 Kcal/kg bw; 1 g protein/kg bw) supplemented with Aminotrofic© 2 packs per day (1 pack = 4 g amino acids) for a period of 3 months. The diet provided 55% energy as carbohydrate, 15% as protein, and 30% as lipids. The amino acid composition of Aminotrofic is as follows: L-leucine (1250 mg), L-lysine (650 mg), L-isoleucine (625 mg), L-valine (625 mg), L-threonine (350 mg), L-cystine (150 mg), L-histidine (150 mg), L-phenylalanine (100 mg), L-methionine (50 mg), L-tyrosine (30 mg), and L-tryptophan (20 mg).
Oral Aminotrofic had to be taken between meals. At the beginning and end of the study all participants underwent a medical examination, a dietician interview to assess nutritional habits and provide nutritional education, blood tests, and body composition assessment by total-body dual-energy x-ray absorptiometry (DEXA).
Body weight and adherence to the diet were assessed 6 weeks from the beginning of the study and at the end of the study. Each eligible participant gave written informed consent.

Measurements

The anthropometric parameters evaluated at the beginning and end of the study included body weight, BMI, fat mass and fat-free mass. Fat mass and fat free mass were assessed as FAT and LEAN mass by DEXA using a Hologic QDR-series total-body scanner.
Biochemical parameters such as blood glucose, total protein, albumin, serum iron, transferrin, glycosylated hemoglobin, and insulin were assessed by standard laboratory techniques at the beginning and end of the study.

Statistical analysis

The statistical parameters were calculated with Microsoft Excel 2000.
The comparisons of the data obtained at the beginning and the end of the study were analyzed using Student's t-test for paired data. The 2-tailed significance threshold was set at $p<0.05$.

RESULTS

All 10 patients completed the study. Their characteristics are presented in Table I. The mean age of the women was higher than that of the men but the difference was not statistically significant. The mean weight and BMI of the study participants were 50.7 ± 7.8 kg and 17.8 ± 1.7, respectively; men had a higher mean weight and BMI than women, but the difference was not statistically significant. All other anthropometric and blood parameters did not show any significant gender difference. At T1 we observed a modest increase in the mean values of all parameters except BCM, FAT and HbA1c (Tab. II). The increase was statistically significant for the following parameters: total protein ($p=0.005$), albumin ($p=0.048$) and insulin ($p=0.022$).

DISCUSSION

As evidenced by the results, supplementation with oral amino acids in malnourished HIV patients did not obtain the highlighted changes in fat-free mass yet led to a significant increase in total protein, albumin and plasma insulin after 3 months of treatment. This finding may have some clinical implications in the light of what emerges from a series of experimental observations.
We must first consider that under conditions of malnutrition associated with HIV infection, the metabolism is oriented toward hypercatabolism probably through changes in the hormone setting produced by the endocrine system (14).

TABLE I - BASELINE PHYSICAL CHARACTERISTICS AND METABOLIC PROFILE OF THE PATIENTS

	Females	Males	P value	All subjects
Number	5	5		10
Age	46.2 ± 7.8	42.5 ± 5.0	NS	45.1 ± 6.3
Height (m)	1.64 ± 0.07	1.73 ± 0.09	NS	1.68 ± 0.09
Weight (kg)	46.3 ± 4.1	55.0 ± 8.4	NS	50.7 ± 7.8
BMI (kg/m²)	17.3 ± 1.7	18.3 ± 1.7	NS	17.8 ± 1.7
BCM (kg)	1.7 ± 0.4	2.1 ± 0.6	NS	1.9 ± 0.5
FAT (kg)	7.9 ± 1.9	6.9 ± 3.4	NS	7.4 ± 2.6
LEAN (kg)	37.0 ± 4.5	46.1 ± 8.7	NS	41.5 ± 8.1
Proteins (g/L)	7.4 ± 0.4	7.7 ± 0.9	NS	7.6 ± 0.6
Albumin (g/L)	4.3 ± 0.4	4.2 ± 0.5	NS	4.3 ± 0.4
Serum iron (µg/dL)	73.2 ± 39.0	102.6 ± 49.1	NS	87.9 ± 44.6
Transferrin (g/L)	2.6 ± 0.52	2.2 ± 0.3	NS	2.4 ± 0.5
Glycemia (mg/dL)	89.2 ± 4.5	87.4 ± 1.7	NS	88.3 ± 3.4
HbA1c (%)	4.9 ± 0.6	5.3 ± 0.5	NS	5.1 ± 0.6
Insulin (µU/mL)	9.1 ± 6.3	9.9 ± 5.1	NS	9.5 ± 5.4

BMI, body mass index; BCM, body cell mass; FAT, fat mass; LEAN, fat-free mass; NS, not significant

TABLE II - MEAN VALUES OF ANTHROPOMETRIC PARAMETERS AND BLOOD CHEMISTRY AT THE BEGINNING (T0) AND END OF THE STUDY (T1)

	T0	T1	
Age (years)	45.1 ± 6.3	-	NS
Height (m)	1.68 ± 0.09	-	NS
Weight (kg)	50.7 ± 7.8	51.0 ± 7.6	NS
BMI (kg/m²)	17.8 ± 1.7	17.9 ± 1.7	NS
BCM (kg)	1.9 ± 0.5	1.9 ± 0.5	NS
FAT (kg)	7.4 ± 2.6	7.2 ± 2.4	NS
LEAN (kg)	41.5 ± 8.1	41.7 ± 8.2	NS
Serum protein (g/L)	7.6 ± 0.6	7.9 ± 0.6	p=0.0051**
Albumin (g/L)	4.3 ± 0.4	4.7 ± 0.4	p=0.0484*
Serum iron (µg/dL)	87.9 ± 44.6	91.4 ± 41.4	NS
Transferrin (g/L)	2.4 ± 0.5	2.7 ± 0.5	NS
Glycemia (mg/dL)	88.3 ± 3.4	88.5 ± 4.3	NS
HbA1c (%)	5.1 ± 0.6	5.1 ± 0.4	NS
Insulin (µU/mL)	9.5 ± 5.4	10.7 ± 5.4	p=0.0221*
HOMA index	1.9 ± 1.4	2.1 ± 1.3	NS

*p<0.05
**p<0.01
BMI, body mass index; BCM, body cell mass; FAT, fat mass; LEAN, fat-free mass; HOMA, homeostatic model assessment; NS, not significant

Wichtig Editore - © 2012 SINPE-GASAPE - ISSN 1828-6232

In such conditions an increase in muscle protein turnover and in the synthesis of inflammatory proteins has been reported (15).

Systemic inflammation contributes to the activation of both proteolysis-inducing factors, such as inflammatory cytokines (TNF-α, interleukin-1β, interleukin-6) and counterregulatory hormones (catecholamines, cortisol and glucagon) and also leads to a decreased activity of anabolic factors such as insulin, growth hormone and IGF-1 (16-19). In addition, TNF-α seems to play an important role in the pathogenesis of insulin resistance by reducing the phosphorylation of tyrosine (20, 21). Given this hypercatabolic framework, preliminary data suggest that high concentrations of amino acids are able to activate both cytoplasmic and mitochondrial protein synthesis and that oral supplementation of a mixture of amino acids may increase the number and volume of mitochondria (22). Furthermore, oral supplementation of amino acids improves insulin resistance and myocardial function in diabetic patients (12, 23). These effects seem to be based on the activation of non-insulin-dependent metabolic pathways that are silent in physiological conditions but can be activated by external stimuli when the insulin-dependent pathway is damaged (24).

Another benefit of supplementation with free amino acids is that they do not require any metabolic process, therefore saving a significant amount of ATP that can be employed to improve the efficiency of digestion (25). Free amino acids are also readily absorbed into the bloodstream and transported into cells by specific carriers, without consumption of ATP (26).

Inside the cell, amino acids cannot be simply regarded as building blocks for protein synthesis since they act as signals regulating cellular functions such as maintenance of muscle protein deposits: this happens through various mechanisms including the inhibition of the catabolic hormone-mediated stimulus (27, 28).

Finally, it is known that some amino acids exert specific functional activities. Leucine, for example, is a potent activator of protein synthesis in skeletal muscle (29). Studies in young adult and older rats have shown that the lack of postprandial anabolism of skeletal muscle occurring during aging is attributable to a decreased sensitivity to leucine (30) and that a leucine meal supplementation is able to restore the rate of protein synthesis in the muscles of older rats (31). In this context it is noteworthy that the amino acid formula under study contains more than 30% of leucine.

The results of this study suggest that oral supplementation with free amino acids for 3 months can improve protein deposits of malnourished HIV patients, although DEXA examination failed to highlight significant changes in lean body mass.

Nevertheless, the moderate but significant increase in total protein and albumin in plasma may be related to an improvement of the catabolic process that characterizes malnutrition associated with HIV. The significant increase in insulin levels may be interpreted as an enhancement of the anabolic stimulus.

Some limitations in the design of this study such as the small number of subjects and the lack of a control group should be taken into account when interpreting the results, assigning them an exploratory nature.

CONCLUSIONS

In this study a balanced diet supplemented with an oral amino acid formula given for 3 months has led to a significant increase in total protein, albumin and insulin. Future research designed to test the hypothesis generated in the present study should consider a greater number of patients, a control group, and a longer period of treatment. Furthermore, in order to promote the anabolic action of leucine on skeletal muscle in the postprandial period, as reported by previous studies on rats, the amino acid formula should be given during meals rather than in between meals.

ACKNOWLEDGMENTS

We express our sincere thanks and gratitude to Professor Michela Zanetti, Dipartimento di Scienze Cliniche, Morfologiche e Tecnologiche, Ospedale di Cattinara, Clinica Medica, Trieste.

Conflict of interest statement: none declared.
Financial support: none.

Address for correspondence:
Dr. Fulvio Muzio
Servizio di Dietologia e Nutrizione Clinica
Azienda Ospedaliera Universitaria "Luigi Sacco"
Via G.B. Grassi 74
20157 Milan, Italy
e-mail: muzio.fulvio@hsacco.it

REFERENCES

1. Chlebowski RT. Significance of altered nutritional status in acquired immune deficiency syndrome. Nutr Cancer 1985; 7: 85-91.
2. Centers for Disease Control and Prevention. Classification system for human T-lymphotrophic virus type III/ lymphadenopathy-associated virus infections. MMWR 1986; 35: 334-9.
3. Hoover DR. Clinical manifestations of AIDS in the era of pneumocystic prophylaxis. N Engl J Med 1993; 329: 1922-6.
4. Paton NI, Sangeetha S, Earnest A, Bellamy R. The impact of malnutrition on survival and the CD4 count response in HIV-infected patients starting antiretroviral therapy. HIV Med 2006; 7: 232-330.
5. Moldaver LL, Sattler FR. Human immunodeficiency virus-associated wasting and mechanisms of cachexia associated with inflammation. Semin Oncol 1998; 25 (Suppl 1): 73-81.
6. Tisdale MJ. Wasting in cancer. J Nutr 1999; 129 (Suppl 1): 243S-6S.
7. Farber MO, Mannix ET. Tissue wasting in patients with chronic obstructive pulmonary disease. Neurol Clin 2000; 18: 245-62.
8. Reid MB, Li YP. Tumor necrosis factor-alpha and muscle wasting: a cellular perspective. Respir Res 2001; 2: 269-72.
9. Li X, Youngblood GI, Payne AH, Hales DB. Tumor necrosis factor-alpha inhibition of 17 alpha-hydroxylase/C17-20 lyase gene (cyp17) expression. Endocrinology 1995; 136: 3519-26.
10. Suttman U, Selberg O, GallatiH, Ockenga J, Deicher H, Mulier MJ. Tumor necrosis factor receptor levels are linked to the acute-phase response and malnutrition in human-immunodeficiency-virus infected patients. Clin Sci 1994; 86: 461-7.
11. Roubenoff R, Grinspoon S, Skolnik PR, et al. Role of cytokines and testosterone in regulating lean body mass and resting energy expenditure in HIV-infected men. Am J Physiol Endocrinol Metab 2002; 283: E138-45.
12. Solerte SB, Gazzaruso C, Schifino N, et al. Metabolic effects of orally administered amino acid mixture in elderly subjects with poorly controlled type 2 diabetes mellitus. Am J Cardiol 2004; 93 (S): 23A-9A.
13. Paddon-Jones D, Sheffield-Moore M, Zhang XJ, et al. Amino acid ingestion improves muscle protein synthesis in the young and elderly. Am J Physiol Endocrinol Metab 2004; 286: E321-8.
14. Dudgeon WD, Phillips KD, Carson JA, Brewer RB, Durstine JL, Hand GA. Counteracting muscle wasting in HIV-infected individuals. HIV Med 2006; 7: 299-310.
15. Baracos VE. Hypercatabolism and hypermetabolism in wasting states. Curr Opin Clin Nutr Metab Care 2002; 5: 237-9.
16. Mourkioti F, Rosenthal N. IGF-1. Inflammation and stem cells: interactions during muscle regeneration. Trends Immunol 2005; 26: 535-42.
17. Prisk V, Huard J. Muscle injuries and repair: the role of prostaglandins and inflammation. Histol Histopathol 2003; 18: 1243-56.
18. Tidball JG. Inflammatory processes in muscle injury and repair. Am J Physiol Regul Integr Comp Physiol 2005; 288: R345-53.
19. Huard J, Li Y, Fu FH. Muscle injuries and repair: current trends in research. J Bone Joint Surg Am 2002; 84A: 822-32.
20. Aljada A, Ghanim H, Assian E, Dandona P. Tumor necrosis factor-alpha inhibits insulin-induced increase in endothelial nitric oxide synthase and reduces insulin receptor content and phosphorylation in human aortic endothelial cells. Metabolism 2002; 51: 487-91.
21. Mark PE, Raghavan M. Stress-hyperglycemia, insulin and immunomodulation in sepsis. Intensive Care Medicine 2004, 30: 748-56.
22. Nisoli E, Cozzi V, Carruba MO. Amino acids and mitochondrial biogenesis. Am J Cardiol 2008; 101 (Suppl): 22E-5E.
23. Scognamiglio R, Negut C, Piccolotto R, Dioguardi FS, Tiengo A, Avogaro A. Effects of oral amino acid supplementation on myocardial function in patients with type 2 diabetes mellitus. Am Heart J 2004; 147: 1106-12.
24. Flati V, Pasini E, D'Antona G, Speca S, Toniato E, Martinotti S. Intracellular mechanism of metabolism regulation: the role of signalling via the mammalian target of rapamycin pathway and other routes. Am J Cardiol 2008; 101 (Suppl): 16E-21E.
25. Pasini E, Aquilani R, Dioguardi F. Amino acids: chemistry and metabolism in normal and hypercatabolic state. Am J Cardiol 2004; 93(S): 3A-5A.
26. Pasini E, Aquilani R, Gheorghiade M, Dioguardi FS. Malnutrition, muscle wasting and cachexia in chronic heart failure: the nutritional approach. Ital Heart J 2003; 4: 232-5.
27. Wolfe RR. Effects of amino acid intake on anabolic processes. J Appl Physiol 2001; 26 (Suppl): S220-7.
28. Volpi E, Ferrando AA, Yeckel CW, Tipton KD, Wolfe RR. Exogenous amino acid stimulates net muscle protein synthesis in the elderly. J Clin Invest 1998; 101: 200-7.
29. Jefferson LS, Kimball SR. Amino acid regulation of gene expression. J Nutr 2001; 131 (Suppl): 2460S-6S.
30. Dardevet D, Sornet C, Balage M, et al. Stimulation of in vitro rat muscle protein synthesis by leucine decreases with age. J Nutr 2000; 130: 2630-5.
31. Dardevet D, Sorn C, Boyle G, et al. Postprandial stimulation of muscle protein synthesis in old rats can be restored by a leucine-supplemented meal. J Nutr 2002; 132: 95-100.

Wichtig Editore - © 2012 SINPE-GASAPE - ISSN 1828-6232