Nutrition 57 (2019) 231–236

Contents lists available at ScienceDirect

Nutrition

journal homepage: www.nutritionjrnl.com

Applied nutritional investigation

Amino acid profile after oral nutritional supplementation in hemodialysis patients with protein-energy wasting

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ARTICLE INFO

Article History:
Received 28 November 2017
Received in revised form 21 May 2018
Accepted 29 June 2018

Keywords:
hemodialysis
amino acids
malnutrition
oral supplements

ABSTRACT

Objectives: Protein-energy wasting (PEW) is highly prevalent in patients on hemodialysis (HD). Oral nutritional supplementation (ONS) is recommended for malnourished patients on HD. The aim of this study was to evaluate ONS on plasma amino acid in HD patients with PEW.
Methods: Thirty-two HD patients with a mean age 59.1 ± 9.5 y with PEW were enrolled into the study. Patients were prescribed ONS (125 mL twice a day for 3 mo) together with dietary advice. The nutritional status was evaluated by means of body mass index, Subjective Global Assessment, and serum albumin and prealbumin levels. The percentages of body fat and lean body mass were measured by means of the near-infrared method. The lean body mass-to-body weight ratios were calculated. Tumor necrosis factor, interleukin-6 and high-sensitivity C-reactive protein, were measured by the enzyme-linked immunosorbent assay method. Serum concentrations of amino acids were measured by the high-performance liquid chromatography method.
Results: After 3 mo of ONS, a significant increase of both serum prealbumin and albumin was observed. The concentration of most of the amino acids increased independently on inflammation.
Conclusions: Dietary advice, combined with ONS, is effective in HD patients with PEW. Both dietary advice and ONS are needed to be sure that patients consume an adequate daily amount of calories and protein.

Introduction

Some studies have shown abnormalities of nutritional status in patients with chronic kidney disease (CKD) [1,2]. Protein-energy wasting (PEW) is highly prevalent in patients on hemodialysis (HD) [3,4]. The underlying mechanisms of PEW are complex, but metabolic derangements related both to exaggerated protein degradation and decreased protein synthesis are of utmost importance [5–8]. Homeostasis between protein synthesis and degradation depends on protein intake and utilization. Accelerated protein degradation, without a sufficient protein supply, may lead to skeletal muscle wasting [9]. In malnourished HD patients, oral nutritional supplementation (ONS) is recommended if nutritional counseling does not achieve an increase in nutrient intake [10–13]. ONS usually supplies calories from fat and carbohydrates, protein (in the form of amino acids and peptides), vitamins, and trace elements.

The aim of this study was to evaluate oral nutritional supplementation with plasma amino acids (AAs) in HD patients simultaneously receiving dietary advice.

Materials and methods

Patients

The study included 32 HD patients (M 19/F 13) with a mean age of 59.1 ± 9.5 y (range 35–86 y), who signed a consent form, were included in the study. Permission for the study was obtained from the Local Ethics Committee in the Medical University of Gdansk.

Inclusion and exclusion criteria

Inclusion criteria for this study were as follows: age ≥18 y, HD treatment for ≥3 mo, absence of infection, written informed consent, and ability to understand the study protocol.

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https://doi.org/10.1016/j.nut.2018.06.013
0899-9007/

Patients with dementia, a life expectancy <6 mo, and who were non-adherent to their dialysis regimen were excluded.

PEW was determined by criteria introduced by the International Society of Renal Nutrition and Metabolism in 2008 [14].

In the present study, the presence of PEW for every patient was assessed according to this definition, using the presence of at least three criteria as an indication of PEW:

1. Serum albumin <3.8 g/dL or serum prealbumin <30 mg/dL,
2. Body mass index (BMI) <23 kg/m^2 or loss of body weight 10% of normal body weight over 6 mo,
3. Subjective Global Assessment (SGA) ≤5.

The studied patients underwent 4 to 5 h of dialysis, three times a week.

In our hemodialysis center, all patients receive dietary recommendations at the beginning of dialysis treatment. In the studied group, all patients again received recommendations typical for hemodialyzed patients. A dietitian advised patients to maintain dietary intake within the recommended range. Nutritional status, as well as anthropometric and biochemical measurements were recorded at the beginning of the study (t = 0), and after 3 mo (t = 1) of ONS.

Nutritional intervention

Patients were treated by oral liquid supplement (drink) dedicated for dialysis patients, at a dose of 125 mL twice a day, for 3 mo. One drink contains 250 kcal and 9.4 g of protein.

The daily amount of the supplement supplied 500 kcal and 18.75 g of protein. It contained carbohydrates, lipids, minerals, trace elements, and vitamins.

To assess patient compliance, for each dialysis session, patients received a fixed number of supplement packets and were instructed to return the unconsumed packets at the next dialysis session.

Nutritional status and anthropometric measurements

Nutritional status was estimated by using the 7-point SGA. The results of the SGA estimation were scored as follows: A score of 7 or 6 indicated good nutritional status, a score between 5 and 3 indicated mild/moderate malnutrition, and a score of 2 or 1 indicated severe malnutrition [15].

Nutritional status was also determined by serum concentration of albumin (using the bromcresol purple method) and prealbumin (using an enzyme-linked immunosorbent assay [ELISA]; Immundiagnostik AG, Bensteim, Germany).

The normalized for body weight protein catabolic rate (nPCR) was calculated according to the following equation:

$$PCR = 0.22 + ([0.036 \times B \times 24]/A)$$

with B representing blood urea nitrogen increase in mg/dL since the last HD; and A the hours since the last HD.

The same scale was used each time the patient was weighed, and the scale was standardized.

The percentage of body loss was calculated according to the following equation: kg lost divided by normal dry weight. The result was multiplied by 100.

BMI was calculated according to the following equation: BMI = body weight/height^2.

The percentages of body fat (%F), and lean body mass (LBM) were measured using the near-infrared method with a Futrex 5000 A (Futrex Inc., Hagerstown, MD, USA). The LBM-to-body weight ratios were calculated.

Biochemical assays

Blood samples were taken from patients fasted overnight, before HD sessions. Samples used for serum collection were allowed to clot at room temperature before centrifugation, and the supernatants were stored at −70°C until further use.

ELISA was used to measure the serum concentration of interleukin (IL)-6 and tumor necrosis factor (TNF; Bender Med Systems GmbH, Austria), as well as serum high-sensitivity C-reactive protein (hsCRP; DRG International Inc., Springfield Township, NJ, USA).

The patients' lipid profiles (total cholesterol, triacylglycerols [TG], high-density lipoprotein cholesterol [HDL-C], and low-density lipoprotein cholesterol [LDL-C]) were measured by routine laboratory methods.

The serum concentrations of 21 AAs were measured by precolumn orthophtaldehyde derivatization using high-performance liquid chromatography (HPLC Hitachi–Merck, Tokio, Japan equipped with a C-18 reversed phase column and a methanol/acetate buffer gradient). Individual peaks were identified from the retention time, and the concentrations were derived from the peak area for appropriate standard and sample solutions. This study includes internal standard analysis to confirm the AA retention time [16].

Statistical analysis

Student's *t* test for comparison of the means between the two groups and the Mann–Whitney U test for nonparametric data were used. Correlations, using Pearson's correlation test, were evaluated (using Statistica, version 12.0; StatSoft, Polska, Krakow, 2016). All the data for the normality of distribution using the Kolmogorov–Smirnov test were analyzed. Data, such as the range, mean ± SD, and median, are expressed.

Cluster analysis was used to classify the data, which were subdivided into groups (clusters), and to better disclose the relationships among the data. Statistically significant differences were defined as $P \leq 0.05$.

Results

Nutritional status

The results of the study group were compared before and after supplementation. The basic characteristics of the study group are shown in Table 1. During the study period, no changes in the glycemic profile were observed in patients with diabetes. Moreover, no significant changes in weight gain were seen between the HD sessions. All the patients were adequately treated, and the Kt/V values were in the reference range.

At the beginning of the study, patients presented low levels of albumin, prealbumin, and body mass loss; SGA indicated deterioration of the nutritional status in the study group (Table 1)

The nutritional status and anthropometric parameters (body weight, BMI, LBM, LBM/body weight ratio, and %F) was stable during the observation period (Table 2).

Furthermore, after 3-mo ONS, significant increases in the serum levels of both prealbumin and albumin, as well as the increase of nPCR, were observed.

The mean serum levels of hsCRP IL-6, and TNF, as well as the lipid profile, did not change during the observation period.

Amino acid profile

Table 3 presents the AA concentrations before and after supplementation.

The concentrations of nine AAs increased statistically significantly after supplementation (see Tables 3 and 4). The greatest increase in the concentrations was observed for histidine (9.47 nmol/100 μL), glutamic acid (8.53 nmol/ 100 μL), and ornithine (7.90 nmol/100 μL).

The concentration of five AAs, glutamine, glycine, methionine, tryptophan, and γ-aminobutyric acid, was decreased after 3 mo of supplementation. Regarding glutamine and methionine, the largest decrease (17.45 nmol/100 μL) with high SD (16.41 nmol/100 μL), was detected.

Table 1
Study group characteristics*

Parameters	Range (N = 32)	Mean (N = 32)	Median (N = 32)
Age (y)	35–86	59.1 ± 9.5	58
M/F	–	19/13	–
Patients with diabetes (n)	–	9	–
Body mass index (kg/m^2)	16.6–40	24.8 ± 4.5	24.5
Kt/V	1.2–1.4	1.3 ± 0.1	1.3
Time of dialysis treatment (mo)	6–324	65.5 ± 74.5	41

*Data presented as means ± SD, median or range.

Table 2
Anthropometrical and biochemical results in the studied group*

Parameters	HD (N = 32) Before (t = 0)	After (t = 1)	*P*-value t = 0 vs t = 1
SGA 7-points	4.7 ± 0.5 5	4.6 ± 0.6 5	0.67
Kt/V	1.3 ± 0.1 1.3	1.4 ± 0.2 1.4	0.89
nPCR g/kg/d	0.93 ± 0.2 0.9	1.04 ± 0.2 1.0	0.07
BMI kg/m^2	24.8 ± 4.8 24.7	24.7 ± 3.7 24.5	0.72
Body weight kg	66.6 ± 11.6 64.5	65.4 ± 13.9 64	0.85
%F	24 ± 6.9 23.7	24.6 ± 6.3 24.1	0.49
LBM kg	51.3 ± 10.2 51.2	51.1 ± 10.3 50.4	0.70
LBM/body weight ratio	0.77 0.79	0.78 0.78	0.88
Albumin g/dL	3.6 ± 2.2 3.8	3.9 ± 5.7 3.9	0.02
Prealbumin mg/dL	9.8 ± 9.1 8.6	15.1 ± 7.7 17.3	0.03
hsCRP mg/l	7.2 ± 3.3 8.3	8.9 ± 7 10	0.82
IL-6 pg/mL	4.2 ± 6.1 1.8	7 ± 10.8 2.2	0.48
TNF pg/mL	5.88 ± 4.8 4.5	5.03 ± 1.7 4.6	0.35
Total cholesterol mg/dL	234 ± 100	227 ± 98	0.48
LDL mg/dL	136 ± 89	145 ± 101	0.52
HDL mg/dL	40.2 ± 16.3 36.6	33.8 ± 12.6 33	0.09
TG mg/dL	205.4 ± 105.8 173.5	198.2 ± 103.9 182	0.54

%F, percent fat; BMI, body mass index; HD, hemodialysis; HDL, high-density lipoprotein; hsCRP, high-sensitivity C-reactive protein; IL, interleukin; LBM, lean body mass; LDL, low-density lipoprotein; nPCR, normalized for body weight protein catabolic rate; SGA, Subjective Global Assessment; TG, triacylglycerols; TNF, tumor necrosis factor
*Data presented as means ± SD and medians.

Table 3
The amino acids concentration in the study group before and after supplementation*

Parameters	Before t = 0	After t = 1	Change
Alanine	23. 15 ± 11.65 23	29.45 ± 28.46 21.4	0.61
γ-aminobutyric acid	3.21 ± 0.77 2.9	1.98 ± 0.44† 1.9	0.01
Arginine	7.83 ± 3.21 6.8	10.36 ± 3.60† 9.9	0.03
Asparagine	1.57 ± 0.55 1.5	2.20 ± 0.67† 2.1	0.02
Aspartic acid	5.15 ± 1.76 5.1	6.00 ± 1.35† 5.4	0.05
Glutamine	49.27 ± 13.66 49.6	31.78 ± 9.84† 32.2	0.04
Glutamic acid	9.40 ± 3.41 9.2	17.8 ± 5.78† 16.2	0.01
Glycine	22.77 ± 8.93 20.4	16.7 ± 7.65† 15.3	0.05
Histidine	10.79 ± 4.55 10.2	20.30 ± 9.57† 17.8	0.02
Isoleucine	4.81 ± 1.87 4.3	4.07 ±1.87 3.7	0.47
Leucine	8.68 ± 2.26 8.5	9.42 ± 3.10 8.8	0.65
Lysine	11.91 ± 3.08 11.7	11.92 ± 3.68 11.3	0.77
Methionine	1.80 ± 0.51 1.7	0.42 ± 0.37† 0.3	0.03
Ornithine	7.91 ± 4.35 7.3	15.85 ± 5.97† 15	0.04
Phenylalanine	5.60 ± 1.52 5.4	5.49 ± 1.51 5.2	0.87
Serine	5.8 ± 2.4 5.4	8.9 ± 9.8† 8.6	0.03
Taurine	11.7 ± 21.9 7	12.9 ± 6.7 10.8	0.07
Threonine	6.32 ± 3.54 5.7	9.64 ± 6.63† 7.6	0.02
Tryptophan	2.49 ± 1.22 2.1	1.83 ± 0.67† 1.6	0.04
Tyrosine	2.28 ± 1.86 2.1	5.02 ± 2.13† 4.2	0.04
Valine	13.2 ± 4.12 12.3	13.15 ± 4.6 12.1	0.67

*Data presented as means ± SD and medians.
†$p<0.05$.

In the case of seven AAs (valine, leucine, alanine, phenylalanine, tyrosine, isoleucine, and lysine), cluster analysis confirmed the results obtained by Student's *t* test. The variability of the concentration of theses AAs before supplementation was similar to that after supplementation, as reflected by their location on the dendrogram (see Fig. 1; in the same clusters, relatively close to each other).

It should be noted that in the case of several other AAs, cluster analysis did not confirm the Student's *t* test results. Five AAs (histidine, glutamic acid, ornithine, threonine, and serine), with concentration changes recognized in the Student's *t* test as statistically significantly different, were set in different clusters.

The differences between the two methods used for analysis of the results can be explained by each of them covering the data in a different way. Cluster analysis considers all the results before and after supplementation, as well as all the variability of the results, not omitting the intragroup variability occurring between individual patients.

Branched-chain AAs

The mean concentration of the AA sum before supplementation was 222.5 nmol/100 μL; it increased to 232.9 nmol/100 μL after supplementation. Additionally, the results obtained with Student's *t* test have shown that changes in the sum of all the AAs, as well as those of branched-chain AAs (BCAAs), were not statistically significant. Before supplementation, the mean concentration of the sum of BCAAs was 26.8 nmol/100 μL; after supplementation, it was 26.7 nmol/100 μL.

Supplementation did not statistically significantly change the ratio of the sum of BCAAs compared with that of the sum of all AAs. Both before and after supplementation, the lowest value was 0.7; after supplementation, the highest value of this ratio increased from 0.17 to 0.19.

Aromatic AAs

The mean concentration of the sum of the aromatic AAs (AAAs) during 3 mo of supplementation increased from 10.16 to 12.35 nmol/100 μL ($P < 0.05$). The AAA sum was more than two times lower than the BCAA sum, and although the AAA concentration was increased significantly, it was still very low.

Because of supplementation, the ratio of the AAA sum to the sum of all AAs was also slightly increased. Before supplementation, the ratio was in the range of 0.03 to 0.07; after supplementation,

Table 4
The results of AA concentration changes in the study group, before and after supplementation ($P < 0.05$)

AA	Change in concentration after supplementation	df	Mean concentration change [nmol/100 μL]	SD (nmol/100 μL)	*t*-value	Critical value
Arginine	Increase	30	2.34	1.98	6.57	2.04
Asparagine		30	0.86	2.26	2.12	2.04
Aspartic acid		30	0.64	0.87	4.07	2.04
Glutamic acid		30	8.53	6.11	7.75	2.04
Histidine		30	9.47	9.76	5.40	2.04
Ornithine		30	7.90	7.97	5.52	2.04
Serine		30	3.44	2.79	6.76	2.04
Taurine		27	3.94	5.38	3.88	2.05
Threonine		30	3.54	7.22	2.73	2.04
Glycine	Decrease	29	4.76	8.03	3.24	2.05
Glutamine		30	17.45	16.41	5.92	2.04
Methionine		28	1.37	0.66	11.15	2.05
Tryptophan		30	0.45	0.59	4.29	2.04
γ-aminobutyric acid		30	0.15	0.05	16.91	2.04

AA, amino acid

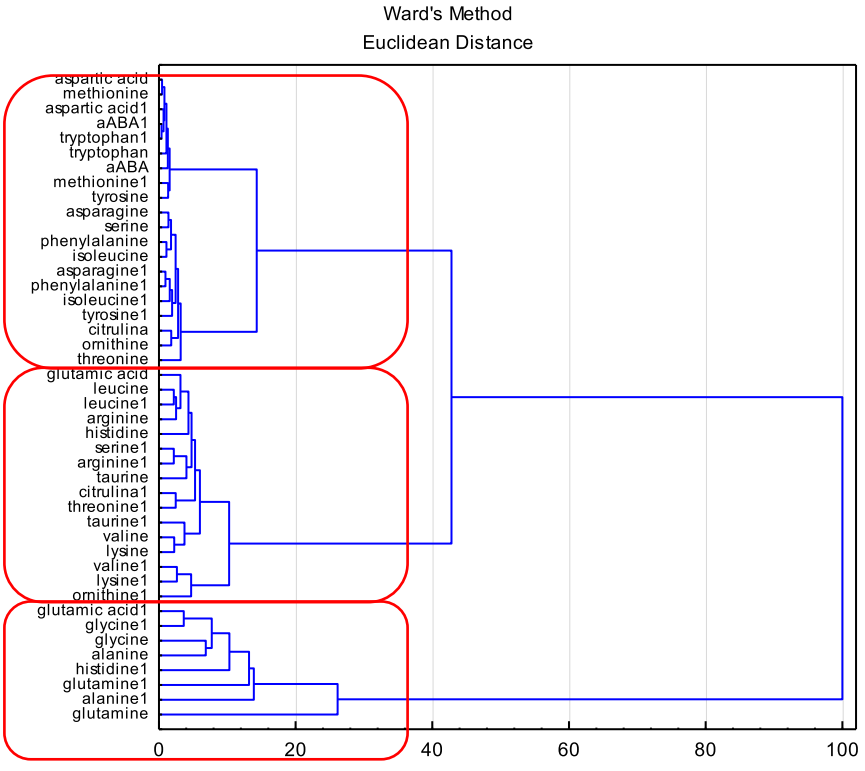

Fig. 1. Cluster analysis results for individual amino acid changes.

the range was 0.04 to 0.11 (the mean values were 0.046 and 0.055 before and after supplementation, respectively).

Inflammation

hsCRP levels for 24 patients in the present study were increased to >5.5 mg/dL (mean value 9.04 ± 1.28 mg/dL) before treatment with ONS. A group of patients with increased hsCRP was characterized by a lower body fat content (28% versus 22.7%; $P < 0.05$). hsCRP levels were correlated positively with the IL-6 and TNF levels ($r = 0.5$ and $r = 0.48$, respectively; $P < 0.05$). Table 5 presents the dependence of the changes in AA concentration during ONS in the study group on the hsCRP level. The statistical analysis did not show significant differences in the AA profile between patients with or without biochemical signs of inflammation (hsCRP >5.5 and ≤5.5 mg/dL, respectively).

Discussion

Multiple treatment strategies to prevent or reverse PEW were studied. Among others, they include continuous nutritional counseling, optimizing the dialysis regimen, preventing or correcting muscle wasting, and the management of comorbidities. Oral or parenteral nutrition supplements, along with appetite stimulators and muscle-enhancing agents, should be prescribed if the patient cannot sustain protein and energy stores despite those efforts [4].

In the present study, dietary counseling and oral supplementation were applied in the group of HD patients with PEW. After 3

Table 5
Direction of changes in AA concentration during supplementation in the study group, depending on hsCRP level ($P < 0.05$)

AA	hsCRP ≤5.5	hsCRP >5.5
Histidine	↑	↑
Glutamic acid	↑	↑
Ornithine	↑	↑
Taurine	↑	↑
Threonine	No changes	↑
Serine	↑	↑
Arginine	↑	↑
Aspartic acid	↑	↑
Asparagine	No changes	No changes
Glutamine	↓	↓
Glycine	No changes	↓
Methionine	↓	↓
Tryptophan	↓	↓
γ-aminobutyric acid	↓	↓

AA, amino acid; hsCRP, high-sensitivity C-reactive protein
↑, increase; ↓, decrease.

mo of ONS, HD patients with PEW showed a significant increase in serum level of prealbumin and albumin, as well as increased nPCR. Their body weight and body composition were stable during the observation period.

The average concentration of the sum of AAs after supplementation was increased compared with the baseline (the AAA sum was increased significantly). The ratio of the sum of BCAAs to that of all AAs did not change, and the ratio of AAA to the total AA slightly increased. The concentration of the AAA sum was more than two times lower than that of the BCAA sum; therefore, even after the ONS, their concentration was still very low.

There were no changes in the concentrations of BCAAs, perhaps because of the short follow-up period. Additionally, BCAAs in the supplement could cause an increased use of AAs in muscle, without a noticeable increase in their concentrations in the plasma of the studied patients. The plasma pool of AAs represents only a small fraction of the total body content for a given AA. For most AAs, the intracellular concentration in the skeletal muscle (the largest pool of free AAs immediately available for protein synthesis) is higher than that in plasma. In patients with CKD, the plasma concentrations of several AAs did not reflect the intracellular concentrations in the muscle cells [17, 18].

On the other hand, the amount of the AAs available in the blood represents major regulatory factors for the promotion of protein synthesis and inhibition of protein breakdown, thus leading to maintenance of muscle mass [19]. The increased supply of AA, in the form of a supplement, could have contributed to the increased protein synthesis. The decrease in the concentrations of some AA observed during the study could be associated with the increased demand.

In the present study, significant increases in histidine were observed after supplementation. At the beginning of the study, the level of histidine was low (10 nmol/100 μL), similar to that in other studies [20, 21]. The observed increase in the histidine concentration could have been advantageous for HD patients. Watanabe et al. [22] suggested that a low plasma concentration of histidine is associated with inflammation, oxidative stress, PEW, and mortality in patients with CKD. Usually renal nutritional supplements are rich in histidine because its concentration is dependent on the availability of dietary protein [20].

PEW is associated with disturbances of AA, as well as other factors, and includes the impairment of skeletal muscle contractile and metabolic and endocrine functions. Currently, AA measurement is not available in clinical practice, but tools for the assessment of muscle mass and strength should be implemented as much as possible. Muscle is the largest protein store in the body. Short-term AA labeling studies suggest that protein supplementation could improve muscle anabolism [23]. However, there is very little data on the effects of protein supplementation on muscle mass in HD patients. In an earlier study of dialysis patients by Beddhu et al. [24], protein supplementation did not affect the muscle mass (not observed, an effect of protein supplementation on the midarm muscle circumference). However, several studies have demonstrated that nutritional supplementation improves nutritional parameters such as the LBM or serum albumin concentration [25,26]. Similarly, in the present study, the LBM was not changed, and albumin and prealbumin were increased during observation. The increase in protein synthesis was the first sign of improvement; some increase in muscle mass occurs over a longer period and is more commonly seen in patients with increased physical activity.

The present study had some limitations such as the short observation period, a relatively small group of patients, and the lack of a thorough assessment of the realization of the dietary recommendations. The observed results concerning the AA concentration could be explained by the various intakes of protein and calories from diet.

Conclusion

We would like to underline that ONS is an effective method of PEW treatment in HD patients, independent of the biochemical signs of inflammation. In HD patients, the loss of AAs with dialysis is observed, so it is important from the clinical point of view to supplement the appropriate AAs in an easy-to-digest and absorb form. The increase in the biochemical markers of the nutritional status and total AAs indicate the effectiveness of the therapy. Further studies on the role of AAs will allow for the optimal composition of protein supplements for dialysis patients. However, both dietary advice and ONS are needed to ensure that patients consume an adequate daily amount of calories and protein.

Acknowledgments

The authors acknowledge Danone Nutricia for the free supply of Renilon 7.5 for patients taking part in this study.

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