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The effects of megestrol acetate on nutrition, inflammation and quality of life in elderly haemodialysis patients

Zhigui Zheng[1] · Jianguo Chen[1] · Dongyuan He[1] · Yuankai Xu[1] · Lili Chen[1] · Ting Zhang[1]

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Abstract

Purpose Malnutrition, inflammation and poor quality of life are prevalent among elderly haemodialysis patients. Megestrol acetate (MA) is a synthetic progestin that is widely used to increase appetite and weight in various clinical settings. MA has been indicated to be effective in improving quality of life in patients with cancers. The aim of the present study was to evaluate the efficacy and safety of MA in treating malnourished elderly haemodialysis patients.

Methods A randomized controlled study involving 46 hypoalbuminemia haemodialysis patients aged 70 years or older was conducted. The patients in MA-treated group ($n=23$) took 160 mg of MA daily, while those in control group ($n=23$) were enrolled without any intervention. Anthropometric parameters and laboratory results, including height, dry weight, body mass index, and modified subjective global assessment score as well as serum albumin, triglyceride, total cholesterol, hsCRP, IL-1b and IL-6 concentrations were measured in all patients before and after the intervention. Health-related quality of life was also evaluated using the KDQOL-SF 1.3.

Results In the MA-treated group, a total of 18 patients finished the therapy over a 3-month period. Appetite was reported as improved by 15 patients, and a statistically significant increase was observed in dry weight (53.36 ± 6.15 vs. 54.24 ± 6.32, $P<0.01$) and serum albumin concentration (29.05 ± 3.91 vs. 37.67 ± 4.88, $P<0.01$) in the MA-treated group compared to those of the control group. The quality of life in both the physical domain (46.73 ± 18.17 vs. 63.37 ± 22.35, $P<0.01$) and the mental domain (50.28 ± 20.36 vs. 68.02 ± 25.48, $P<0.01$) was also improved in the same group. There was no significant change in the inflammatory marker concentrations after the intervention. No serious or unexpected adverse events were observed except that one patient who withdrew due to excessive fluid gain between haemodialysis sessions.

Conclusion Our data suggest that MA can be effective in improving nutritional status and quality of life by increasing appetite in elderly haemodialysis patients with acceptable side effects; however, MA might not ameliorate inflammation.

Keywords Megestrol acetate · Haemodialysis · Malnutrition · Quality of life

Introduction

Due to the development of dialysis techniques and equipment, old age is no longer considered a contraindication for haemodialysis. In recent decades, a steadily increasing number of elderly patients worldwide have been diagnosed with end-stage renal disease (ESRD) and have required haemodialysis [1, 2]. As an effective treatment for patients with ESRD, haemodialysis may prolong life expectancy but may also bring greater burden due to treating patients with comorbidities. Two common clinical problems faced by elderly haemodialysis patients are malnutrition and low quality of life. In recent studies, the incidence of malnutrition in haemodialysis patients has been reported to be 40–60% [3, 4]. This condition is more common among elderly patients [5]. Malnutrition is a clinical issue because of its negative impact on quality of life, comorbidities and hospitalizations, and, more importantly, cardiovascular health, all of which cause mortality by overlapping with inflammation, which is also known as protein-energy wasting syndrome [6].

The main aetiology of malnutrition in ESRD is loss of appetite. Other reasons include the effects of cytokines on the central nervous system, drug–nutrient interactions, the loss of amino acids in every HD session, gastrointestinal diseases and depression [7]. Of note, anorexia itself may

✉ Zhigui Zheng
timdar317@163.com

[1] Department of Nephrology, Zhejiang Hospital, Lingyin road 12, Hangzhou, Zhejiang, People's Republic of China

lead to metabolic disturbances, protein-energy wasting, cachexia, and a significantly higher rate of morbidity and mortality [8]. Furthermore, elderly patients with end-stage kidney disease often have lower quality of life scores on both generic and specific dimensions of the evaluations [9]. All of these factors, including the decline in capacity to perform physical activities, the considerable comorbidities secondary to various chronic diseases, the vascular access complications, the high rate of hospitalizations and the emotional disturbance and social factors could impair quality of life in these patients and deserve special attention in elderly patients [10]. Previous studies have identified the close association between nutritional status and quality of life in ESRD patients [11]. Thus, successful management of malnutrition and anorexia should be conducted in haemodialysis patients not only to increase the long-term survival rate but also to improve health-related quality of life.

Conventional nutritional and metabolic interventions in anorexia and malnutrition of haemodialysis patients do not provide satisfactory results. MA is a synthetic progestin that is widely used to increase appetite and weight in various clinical settings [12]. It is also effective in improving quality of life in patients with cancer [13]. The exact mechanism by which MA exerts its orexigenic and anticachectic effects is still unclear. It is accepted that the drug might work by downregulating the synthesis and secretion of proinflammatory cytokines [12]. Other mechanisms, such as stimulation of neuropeptides, are also believed to be involved [14]. Previous studies have demonstrated the favourable therapeutic effects of MA on the treatment of malnutrition in haemodialysis patients [14–17]. Although side effects, including fluid retention, diarrhoea and hyperglycaemia have been reported at various rates, it is currently agreed that the benefits of MA outweigh the adverse effects. Furthermore, almost all the studies of MA focus on non-elderly patients. Few data on treating malnutrition, inflammation and poor quality of life with MA in elderly haemodialysis patients are available. Hence, we conducted the present study to evaluate the effect and safety of MA in treating this specific group of haemodialysis patients.

Patients and methods

This was a randomized controlled clinical trial conducted by the Nephrology Department of Zhejiang Hospital in China. Seventy-eight patients on chronic haemodialysis were enrolled between May 2016 and July 2018. The inclusion criteria were as follows: (1) patients aged 70 years and over who had undergone maintenance haemodialysis treatment for at least 3 months; and (2) patients with a serum albumin concentration of less than 3.8 g/dL for at least two consecutive months. The exclusion criteria included the following: (1) inadequate haemodialysis as defined as a KT/*V* less than 1.2; (2) concurrent use of glucocorticoids or immunosuppression at the time of beginning treatment with MA; and (3) confirmed central nervous system disease, cancer, severe heart failure, inflammation or gastrointestinal disease that may affect dietary intake. All the subjects provided informed voluntary consent, and the protocol was approved by the local ethics committee.

Patients from two dialysis centres in China who met the inclusion criteria were recruited and randomly (by means of a random number table) assigned to the experimental group and the control group. The experimental group was treated with MA (160 mg per day) in tablet form for 3 months, whereas patients in the control group received nothing except their current treatment.

All patients were from the outpatient department and anuric, undergoing 4-hour sessions of high-flux HD thrice weekly with ultrapure dialysate. Anthropometric parameters included height, dry weight, and body mass index (BMI). Dry weight was evaluated using clinical criteria, and BMI was calculated by the following equation: dry weight (kg)/height squared $\left(\mathrm{m}^2\right)$. The haemodialysis adequacy was assessed by KT/*V*, which was calculated using a standard formula as follows: $\mathrm{spKT}/V = -\ln(R - 0.008.t) + (4 - 3.5 \times R) \times \mathrm{UF}/W$, where UF = ultrafiltration (in litres), W = post-dialysis weight (in kilogrammes), t = duration of dialysis session, R = the ratio of post-dialysis to pre-dialysis BUN, Ct = urea concentration at the end of dialysis session, Co = urea concentration at the start of dialysis session. The hsCRP and cytokine (IL-1β and IL-6) concentrations were measured by high-sensitivity sandwich enzyme-linked immunosorbent assay (ELISA) kits. Appetite was assessed by a 5-point Likert scale (1, very poor; 5, excellent) using the DOPPS questionnaire [18]. The normalized protein catabolic rate (nPCR) was calculated by measuring the interdialytic rise in blood urea nitrogen after a midweek dialysis session. The subjective global assessment (SGA) of nutritional status was performed based on the 7-point SGA scale and consisted of a medical history and physical examination, which included weight change, gastrointestinal symptoms, functional capacity, comorbidity, subcutaneous fat, muscle wasting and oedema. Each domain was rated from 1 to 7, and the overall SGA score was determined. Patients were classified into three groups: A = SGA score 1 to 14 (well nourished), B = SGA score 15 to 35 (mildly to moderately malnourished), or C = SGA score 35 to 49 (severely malnourished). Health-related quality of life was assessed using the kidney disease quality of life-short form (KDQOL-SF) 1.3 for each patient, which contained 43 items on quality of life for renal patients and 36 items on general health [19]. Anthropometric parameters and laboratory values were recorded at baseline and every

month thereafter, while the assessment of SGA and quality of life was completed at baseline and 3 months after the intervention.

Statistical analyses were performed using SPSS version 18.0. We used the Kolmogorov–Smirnov test to assess the normalcy of the distributions. Continuous variables were expressed as the mean ± SD, and Student's *t* test was used to compare the means of normally distributed variables. The Mann–Whitney *U* test was used for abnormally distributed variables between the two groups. To assess the significance of changes in the repeated measures variables in the same group, either one-way ANOVA or nonparametric Friedman's ANOVA was used, and least significant differences tests (post hoc comparisons) were used if necessary. Differences among categorical variables were analysed using the Chi square test. A P value < 0.05 was considered significant for all comparisons.

Results

Figure 1 shows a flow chart of the participants through the study. After exclusion, 46 participants were enrolled from 2 dialysis centres in China. Thirty-nine subjects completed the study, including 18 in the MA-treated group and 21 in the control group. Seven patients dropped out within the 3 months of the study. Among them, two patients (one in each group) died from either cerebral haemorrhage or heart failure. One patient in the MA-treated group was transferred to peritoneal dialysis. Another patient in the control group was excluded from the study because of non-compliance (disregarded the reassessment of quality of life 3 months later). Two other patients in the MA-treated group withdrew due to intolerance to the side effects of the drug, and one patient was lost to follow-up in the same group. Their data were excluded from the analysis. During the intervention phase, two patients in the MA-treated group

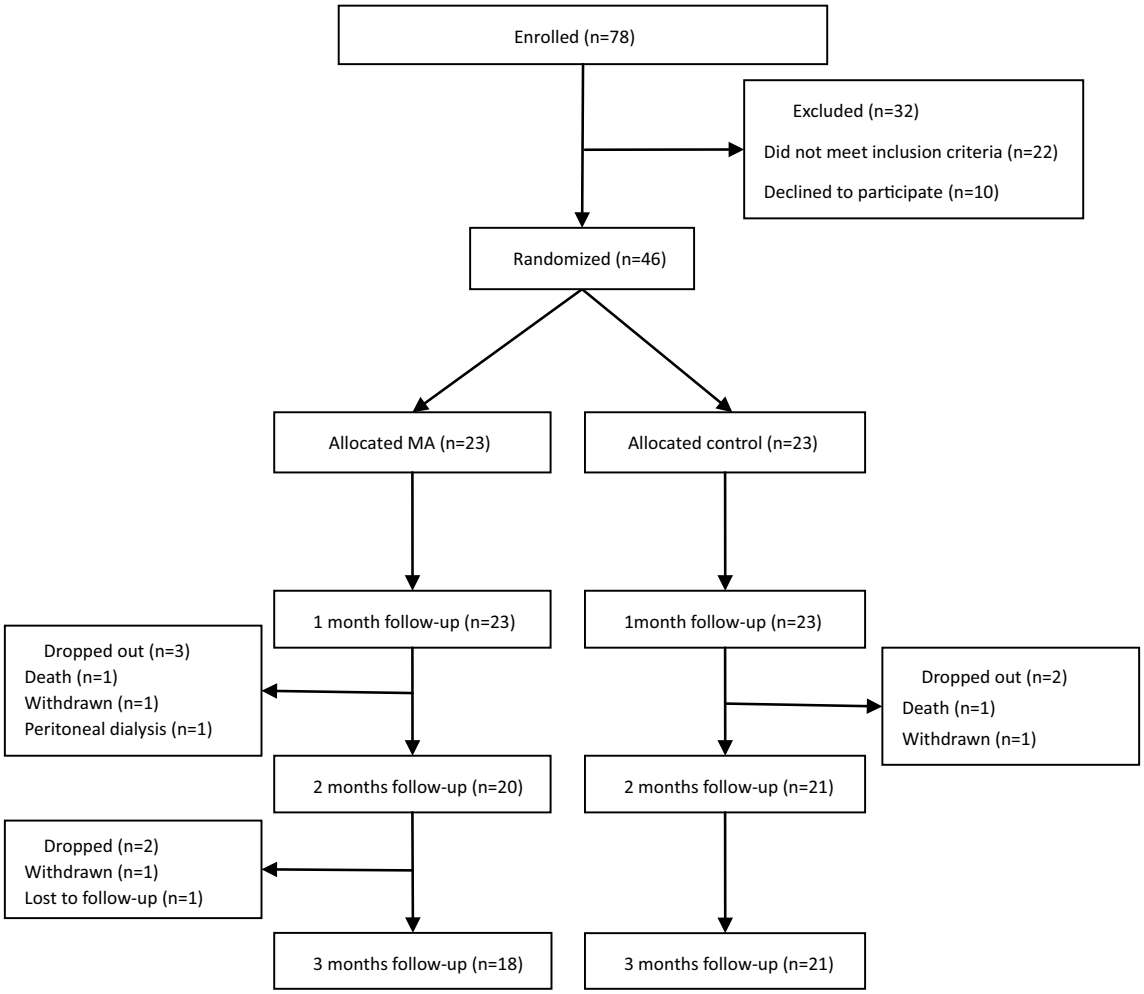

Fig. 1 Flow chart of the participants through the study

required hospital admission that was attributed to community-acquired pneumonia. The treatment with MA was suspended and started after the patients were discharged. There were no significant differences in terms of sex, age, marital status, profession, educational level, income, dialysis dose, cause of disease, duration of haemodialysis, serum albumin or BMI between the two groups. The average ages for the MA-treated group and for the control group were 78.56 ± 5.12 years and 77.4 ± 5.03 years, respectively. Table 1 summarizes the baseline demographic, clinical and laboratory parameters of the MA-treated patients. In the MA-treated group, ten patients (55.6%) were male. The causes of ESRD in the experimental group were as follows: hypertensive nephropathy (8), diabetic nephropathy (4), ischaemic nephropathy (3) and other (3).

Appetite was reported as improved in 15 patients and, was accompanied by a substantial increase in the daily energy intake. As shown in Table 2, the treatment led to statistically significant increase in both dry weight and BMI after 3 months of MA treatment. Of note, the change in both

Table 1 Demographic and clinical characteristics of MA-treated patients

Case	Sex	Age	Protopathy	Vintage (months)	KT/*V*	Dry weight (kg)	BMI (kg/m^2)	Appetite	Albumin (g/L)	nPCR (g/kg/day)	SGA
1	M	82	HTN	12	1.3	57.2	19.58	3	26.43	0.8	C
2	M	78	DN	5	1.5	56.7	22.24	5	23.51	1.1	C
3	F	76	IRD	17	1.7	50.1	17.56	3	25.56	0.9	C
4	F	75	HTN	26	1.6	47.5	17.28	4	30.68	0.7	C
5	F	77	GN	17	1.3	51.7	18.30	2	34.55	0.7	C
6	M	84	AAV	21	1.4	64.7	22.31	4	27.12	0.7	B
7	M	84	HTN	46	1.9	64.8	20.20	4	28.76	1	B
8	F	71	HTN	11	1.4	46.1	17.86	3	25.8	0.9	C
9	M	76	HTN	61	1.5	55.8	21.35	4	33.45	0.6	A
10	M	78	DN	6	1.6	52.1	17.92	2	36.19	0.7	B
11	F	88	GN	38	1.7	43.2	18.55	4	29.04	0.9	C
12	M	71	HTN	28	1.8	52.6	20.56	4	32.86	0.9	B
13	F	79	DN	11	1.3	47.8	21.35	4	31.26	0.9	B
14	M	81	IRD	31	1.2	55.4	21.70	3	27.68	1.1	C
15	M	77	HTN	9	1.4	61.3	24.17	5	29.9	0.7	A
16	F	70	DN	52	1.5	47.1	18.26	4	24.65	0.7	B
17	F	86	IRD	102	1.6	51.2	19.24	3	32.25	0.7	C
18	M	81	HTN	33	1.5	55.2	18.11	2	33.25	1.1	C

DN diabetic nephropathy, *HTN* hypertension, *IRD* ischemic renal disease, *AAV* ANCA-associated vasculitis, *GN* glomerulonephritis

Table 2 Nutritional and inflammatory indices before and after 1 month, 2 months and 3 months of MA administration

Variable (mean ± SD)	Baseline	1 month	2 months	3 months	*P* value
Weight (kg)	53.14 ± 5.71	53.48 ± 6.03	54.11 ± 5.96	55.28 ± 5.97	< 0.05#*
BMI (kg/m^2)	19.81 ± 2.01	19.93 ± 2.04	20.16 ± 2.04	20.60 ± 2.11	< 0.05#*
Albumin (g/dL)	29.05 ± 3.91	30.31 ± 4.29	34.79 ± 4.19	37.67 ± 4.88	< 0.05#*
Pre-dialysis creatinine (mg/dL)	5.34 ± 1.31	5.65 ± 1.27	6.27 ± 1.84	7.58 ± 2.01	< 0.05#*
Fasting blood glucose (mg/dL)	120.12 ± 23.58	123.12 ± 30.24	126.08 ± 38.74	127.58 ± 42.68	NS
Total cholesterol (mg/dL)	184.37 ± 60.91	182.76 ± 59.38	185.22 ± 57.83	180.46 ± 55.26	NS
Triglycerides (mg/dL)	128.76 ± 63.48	134.43 ± 75.25	152.76 ± 70.91	163.76 ± 86.72	< 0.05#
nPCR (g/kg/day)	0.84 ± 0.16	0.86 ± 0.19	0.92 ± 0.21	1.12 ± 0.17	< 0.05#*
HsCRP (mg/L)	7.35 ± 6.22	7.03 ± 6.03	6.84 ± 5.83	7.81 ± 6.57	NS
IL-1β (pg/mL)	2.57 ± 0.78	1.85 ± 0.43	2.35 ± 0.69	1.98 ± 0.55	NS
IL-6 (pg/mL)	17.53 ± 12.46	20.28 ± 16.51	15.79 ± 13.18	18.34 ± 13.56	NS

#Baseline vs. 3 months in MA-treated group

*MA-treated group vs. control group after 3-month intervention

indices showed statistically significant differences within 2 months after starting the MA therapy. Analogously, the increase in dry weight and BMI in the MA-treated group was both significantly higher than those in the control group after the end of the intervention.

According to the results presented in Table 2, a significant increase in serum albumin concentration was also observed beginning in the 2nd month after starting the intervention, and it persisted throughout the next period of the study. Its change between the two groups was significantly different at the end of the 3-month intervention (8.62 ± 4.54 g/L vs. 2.11 ± 0.21 g/L for the MA and control groups, respectively, $P < 0.05$, not shown). Even after the withdrawal of MA, the improved level of serum albumin in 12 patients persisted from 3 to 6 months postintervention (from 38.23 ± 5.16 to 37.85 ± 5.09 g/L, $P > 0.05$, not shown). There was a trend existing towards a gradual increase in the concentration of fasting blood glucose in the MA-treated group which was found to be statistically nonsignificant. The results also showed statistically significant pretreatment and post-treatment differences in triglyceride levels and nPCR in the MA-treated group, while the concentration of cholesterol in the same group did not exhibit any difference after the treatment. Moreover, the number of well-nourished (SGA-A) patients in the MA-treated group increased from two (11.1%) to eight (44.4%) ($P < 0.05$), while the number of severely malnourished (SGA-C) patients markedly decreased from ten (55.6%) to three (16.7%) ($P < 0.05$). We did not find any significant changes in PG-SGA scores in the control group. The average levels of PCR, HsCRP, IL-1β and IL-6 at baseline in all patients were higher compared with the results of the general population ($P < 0.05$ for all, not shown). However, there were insignificant differences in PCR, HsCRP, IL-1β and IL-6 before and after intervention in the MA-treated group ($P < 0.05$ for all), which were similar to the results of the control group (not shown). The changes in weight, BMI, albumin, and pre-dialysis creatinine in the MA group were also found to be significant compared with the control group (details not shown).

As shown in Table 3, no significant difference in mean total scores on the quality of life assessment between the two groups was detected before the intervention. However, after the intervention, the mean quality of life score significantly increased in the MA-treated group compared with

Table 3 Comparison of dimensions of quality of life (KDQOL-SF) between the two groups before and after intervention

	MA-treated group		Control group		*P*
	Baseline	3 months	Baseline	3 months	
ESRD-targeted items					
Symptoms/problems	63.13 ± 12.41	75.46 ± 14.85	62.37 ± 14.25	65.41 ± 15.39	< 0.01#*
Effects of kidney disease	58.30 ± 7.36	59.25 ± 8.36	60.06 ± 10.35	60.77 ± 12.41	0.18
Burden of kidney disease	48.01 ± 13.76	50.24 ± 15.26	49.11 ± 16.92	51.20 ± 13.66	0.27
Work status	17.24 ± 3.35	20.41 ± 9.44	18.17 ± 5.69	19.66 ± 6.43	0.09
Cognitive function	68.32 ± 23.25	71.82 ± 34.57	69.42 ± 25.76	70.22 ± 25.41	0.21
Quality of social interaction	64.15 ± 13.20	72.15 ± 15.91	64.43 ± 15.37	65.11 ± 15.28	< 0.01#*
Sexual function	22.41 ± 5.39	24.08 ± 6.17	21.58 ± 7.18	22.02 ± 7.91	0.21
Sleep	44.33 ± 11.19	46.25 ± 12.24	45.02 ± 14.26	45.86 ± 12.56	0.12
Social support	75.21 ± 28.26	74.36 ± 23.36	73.47 ± 24.33	75.21 ± 25.6	0.38
Dialysis staff encouragement	88.65 ± 15.14	87.57 ± 12.57	86.29 ± 14.82	87.34 ± 12.90	0.42
Patient satisfaction	68.04 ± 12.57	82.01 ± 18.31	69.15 ± 13.35	70.93 ± 14.29	< 0.01#*
SF-36 items					
Physical functioning	45.42 ± 17.53	68.75 ± 24.59	46.18 ± 18.23	45.26 ± 15.68	< 0.01#*
Role physical	42.38 ± 15.26	62.45 ± 29.53	43.52 ± 14.35	45.61 ± 22.46	< 0.01#*
Bodily pain	69.47 ± 23.46	72.69 ± 32.78	71.39 ± 25.67	74.21 ± 28.32	0.12
General health	50.24 ± 23.16	65.62 ± 30.38	51.29 ± 26.78	53.48 ± 23.61	< 0.01#*
Vitality	45.20 ± 12.58	64.66 ± 28.31	46.35 ± 14.72	48.52 ± 20.18	< 0.01#*
Social functioning	65.34 ± 13.11	73.15 ± 16.46	66.42 ± 15.32	68.38 ± 18.66	< 0.01#*
Role emotional	46.53 ± 9.61	67.24 ± 12.36	48.53 ± 9.61	50.24 ± 10.37	< 0.01#*
Mental health	58.58 ± 15.25	65.02 ± 18.38	61.42 ± 17.32	62.35 ± 15.33	< 0.01#*
Physical component summary (PCS)	46.73 ± 18.17	63.37 ± 22.35	48.11 ± 19.80	47.29 ± 20.63	< 0.01#*
Mental component summary (MCS)	50.28 ± 20.36	68.02 ± 25.48	51.77 ± 21.19	52.21 ± 22.04	< 0.01#*

#Baseline vs. 3 months in MA-treated group

*MA-treated group vs. control group after 3-month intervention

the control group. Moreover, the mean quality of life score showed a statistical difference in the MA-treated group by intervention ($P = 0.00$), whereas there was no significant change in the control group ($P = 0.43$). The domains that showed significantly improved scorers in the MA-treated group were physical functioning, role physical, general health, role emotional and vitality.

With regard to the side effects of MA, only two patients withdrew from the MA-treated group due to excessive fluid gain between haemodialysis sessions. One patient died of causes unrelated to the use of MA as mentioned above. The other patients in the MA-treated group tolerated the drug well during the intervention, except for a few mild adverse effects. Excessive weight gain (> 5% of dry weight) before the next haemodialysis session appeared in five subjects, whereas none of them suffered from congestive heart failure or severe hypertension. Two patients with diabetes mellitus required their insulin dosage to be modified after a 2-month administration of MA. We also found that triglyceride levels concurrently increased in eight patients in this group.

Discussion

Anorexia, always accompanied by malnutrition, is a very common issue in elderly haemodialysis patients and its prevalence is steadily increasing according to the literature [17, 20]. Anorexia is a strong predictor of quality of life in haemodialysis patients, contributing to an excessively high rate of mortality and hospitalization in this group [20, 21]. However, there is still a lack of an effective therapeutic agent that could be used to correct anorexia and/or malnutrition without any side effects among haemodialysis patients. Despite controversies, a certain number of previous studies have demonstrated that MA could be one choice for treating malnutrition and improving quality of life [17]. Our data also indicate that MA, with a dosage of 160 mg once daily, is also an effective therapeutic agent in reversing malnutrition and improving quality of life in elderly haemodialysis patients without severe adverse effects.

Recent studies found that MA may be effective in improving appetite, caloric intake and nutritional status in ESRD patients [14–16]. The underlying exact mechanisms by which MA works remain obscure. According to results obtained from animal experiments, MA may induce appetite via stimulation of neuropeptide Y in the hypothalamus as well as via calcium channels in the ventromedial hypothalamus [22, 23]. It is also widely accepted that MA has glucocorticoid-like activity [24], making it a potential mechanism for upregulating albumin gene expression and increasing albumin synthesis in vivo. In addition, it has also been suggested that MA may work by downregulating proinflammatory cytokines such as IL-1, IL-6, and TNF-α, further inhibiting cytokine-dependent inflammatory processes [15].

Our data suggest an improved appetite and a trend towards a gradual increase in dry weight, BMI and serum albumin levels at the end of the 3-month observation period. This finding is in accordance with the results of previous studies that did not specifically focus on elderly haemodialysis patients [15, 17, 25]. Besides, we found an increase in weight, and BMI was similar between diabetic patients and non-diabetic patients despite our limited sample size. This indicates that MA might also work for malnourished elderly diabetic patients. Surprisingly, the improved level of serum albumin in 12 patients persisted from 3 to 6 months after the start of the intervention even after the withdrawal of MA. Since hypoalbuminemia develops in a large number of elderly haemodialysis patients, it has become a powerful predictor of clinical outcomes in this population, and its increase may bring lower overall mortality. In contrast to the results of the study conducted by Justyna et al. [15], a trend towards an increase in the concentration of triglycerides in our study was observed, which became statistically significant during the 2nd month of treatment. We presume that this finding may be mainly attributed to the improvement of appetite, which was followed by the change of nutritional status.

Protein-energy wasting syndrome is widely prevalent among haemodialysis patients and is one of the major causes of cardiovascular disease, hospitalization and mortality, especially in elderly populations [26, 27]. Zahra et al. [6] found that protein-energy wasting syndrome is also considered to be highly correlated with quality of life among HD patients in both the physical and mental domains. Our study also indicated that cytokine levels in all patients were relevantly higher at baseline compared with those of the general population. Nevertheless, the concentrations of IL-6, IL-1, and CRP remained unchanged after 3 months of exposure to MA, which is in contrast to its anti-inflammatory properties. To our knowledge, the results are in agreement with the present study and are complementary to other results for elderly haemodialysis patients [14, 15, 28]. Multiple reasons may be involved in this contradictory phenomenon. First, inflammatory mediators/biomarkers are considered to have certain volatility both in the general population and among haemodialysis patients because of various confounders. Advanced age, ESRD, infection and malnutrition could all be influencing factors, making them potentially unstable clinical indices. Second, it is widely accepted that MA mainly increases fat mass, and the adipose tissue itself is an active endocrine organ secreting proinflammatory adipokines [29]. Third, haemodialysis patients are significantly more likely to suffer from infectious complications due to

weakened immune reactivity and additional risk factors such as fistula or catheter infections.

It is now widely accepted that patients undergoing haemodialysis tend to have a significant level of impairment in their quality of life, and it is worse among elderly patients [9, 10]. We found a similar result of the diminished quality of life scores in this group, both in the physical and the mental domains. This change in quality of life score might be influenced by multiple factors, such as the change of life pattern caused by haemodialysis, decreased physical viability, increased presence of more common chronic diseases and related complications as well as the high rate of depression [30]. Preceding researches have confirmed the efficacy of MA in improving the quality of life in cancer patients [31]. However, there are controversies regarding its positive effect on ameliorating the quality of life in haemodialysis patients. In the study by Justyna et al. [15], the authors reported an insignificant change in the quality of life of dialysis patients after 6 months of MA administration. Nevertheless, in another double-blind, placebo-controlled study, greater improvement in ability to exercise over 24 weeks in the MA group compared to that of the placebo group was found based on the Borg RPE scale [17]. We evaluated the quality of life of elderly haemodialysis patients using ESRD-targeted SF-36 items and surprisingly observed that MA had significant effects on several dimensions of quality of life, including the quality of social interaction, physical functioning, vitality, mental health and social functioning. Two reasons may have accounted for this contradiction of results: one is the small sample size of all the relative studies, which may limit any definitive conclusion, and the other is the lack of a universally accepted criterion for assessing the quality of life as well as the difficulty in precisely defining and measuring it. Further large-scale multicentre studies are warranted to elucidate whether MA could improve the quality of life in ESRD patients, especially elderly patients.

In our study, no serious or unexpected adverse events were observed with MA at a dose of 160 mg/day in malnourished elderly haemodialysis patients throughout the clinical trial. The main reason for the premature termination of patients' participation was non-compliance with the therapeutic recommendations. Only one patient discontinued the study due to excessive fluid gain between dialysis sessions. To some extent, this may also be associated with poor adherence to the restriction on fluid intake. The encouraging result of the low incidence of adverse reactions is consistent with the previous finding conducted by Meenakshi et al. [28], although it is in contrast to other studies [15]. One of the major contributors to this finding may be the low dose of MA we used in treating the target patients. To improve compliance with the therapy, strict dietary instructions were followed, including avoiding excessive fluid intake, and patients participating in all educational programmes throughout the intervention process. This could also be a contributor to results as good as we found. Therefore, the findings of our study indicate that 160 mg/day may be an optimal dosage for treating elderly ESRD patients.

Limitations of this study should be addressed as follows: first, the small sample size limits the ability of the study to draw definitive conclusions for changes in nutritional and inflammatory indices and quality of life. Second, an analysis of body composition changes was not performed because of the limited technology, so whether MA ultimately increased muscle mass or fat mass was not confirmed. Third, one of the adverse effects caused by MA is adrenal insufficiency, especially in those who have taken MA for a long term. We did not detect the concentration of ACTH or cortisol levels due to a lack of symptoms, which may omit asymptomatic patients who had already experienced adrenal insufficiency. Fourth, no placebo was administered in the control group, which may affect the results since psychological factors may influence appetite. In addition, interpersonal variability in the process of assessing quality of life might have affected the accuracy of the data collected.

In conclusion, our results demonstrated that administering MA at a dosage of 160 mg/day could improve nutritional status and quality of life by increasing appetite in elderly malnourished haemodialysis patients without serious or unexpected adverse events, although inflammation was not inhibited. Therefore, we cautiously recommend using MA at such a low dose for treating anorexia or malnourished elderly haemodialysis patients to improve their nutritional status and quality of life. Further large-scale multicentre studies are required to confirm the effects and safety of MA in treating haemodialysis patients.

Compliance with ethical standards

Conflict of interest The authors declare that they have no conflict of interest.

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