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Role of alpha-lipoic acid in protection from cardiovascular events in patients with hemodialysis

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Abstract:

Background: The leading cause of death in patients on hemodialysis (HD) is cardiovascular events (CVEs). Objective: This study aimed to assess the protective effects of alpha-lipoic acid against possible CVEs. Methods: 70 HD patients were randomly allocated into two groups, tested and control groups; in a randomized clinical study. The tested group received ALA supplementation, a daily capsule of 600 mg, whereas the control group received placebo capsules daily for 3 months. Serum levels of AGEs, Fe, hemoglobin (Hb), ferritin, and total iron-binding capacity were detected in both groups before and after treatment. **Results:** No significant differences in age, sex, duration of dialysis, and contributing factors for dialysis were found between both groups ($P>0.05$). After three months of ALA intervention, AGEs serum levels were significantly reduced. On the other hand, serum levels of adiponectin, Fe, and Hb were significantly increased in the tested group compared to the control group ($P < 0.05$). ALA did not affect lipid profiles including triglycerides, total cholesterol, HDL-C, and LDL-C.

Conclusions: The use of alpha-lipoic acid in patients with HD may lead to a decrease in the chance of atherosclerosis progression, and so decrease in CVEs. We recommend that alpha-lipoic acid should be one of the corner stores in the management of HD patients.

Key words: Alpha-lipoic acid (ALA)**,** Adiponectin, cardiovascular events (CVEs), hemodialysis (HD), advanced glycation end products (AGEs).

Introduction

Cardiovascular events are the prominent cause of death in patients with end-stage renal disease (ESRD), accounting for approximately 40% of total mortality [1]. Dyslipidemia which is an overbearing cardiovascular risk factor in these patients [2], and is further usually conveyed in patients with chronic kidney disease (CKD) [3]. Other risk factors such as inflammation [4] and oxidative stress [5] have fascinated significant attention for CV events in CKD patients. The direct relationship between oxidative stress and inflammation has been exposed in many studies [5; 6]. Consequently, the administration of antioxidant supplements would make a substantial impact on reducing the incidence of CV events by improving the oxidative stress and inflammation in these patients.

Cardiovascular complications have been accompanied by long-term hyperglycemia, including the development and advancement of coronary artery diseases (CAD) in diabetic people. Nevertheless, the serious role of metabolic memory in the pathogenesis of atherosclerosis and cardiovascular disease, regardless of correction of hyperglycemia, has been confirmed in recent studies [7].

Advanced glycation end products (AGEs), which are generated from endogenous or exogenous sources are key mediators of metabolic memory, displaying a critical cardiometabolic effect in both diabetic and non-diabetic patients [8; 9]. During normal aging and physiological metabolism, the endogenous formation of AGEs happens primarily through the non-enzymatic glycation of proteins, known as the Maillard reaction [7].

Synthesis of AGE results in the development of α-dicarbonyls, such as methylglyoxal (MG) and glyoxal (GL), glyceraldehyde, and 3-deoxyglucosone, which further react with proteins in the circulation to form more AGEs molecules [8; 9]. The main source of AGEs formation is the Maillard reaction. Further oxidation and dehydration reactions accompanied by widespread crosslinking take place to generate more complex structures, the cross-linked AGEs [10; 11]. Alpha-lipoic acid (ALA) is a naturally stirring compound acts as a strong antioxidant that is rapidly absorbed. [12] Many previous studies on animals [13; 14] have revealed that ALA also has anti-inflammatory effects in various systems. On the other hand, in human studies, the antioxidant and anti-inflammatory properties of ALA have been not as much investigated, especially in patients undergoing hemodialysis (HD). Advanced glycation end products (AGEs), are generally eliminated by the kidney, formed by the non-enzymatic reaction between protein molecules and reducing sugars. Accumulation of these compounds increases oxidative reactions, causing inflammation leading to fibrosis, vascular damage, and hastening atherosclerosis [16].

In chronic renal failure, AGEs accumulation in the tissue due to decreased excretion was associated with increased vascular stiffness [17]. Koska et al. showed that increased levels of AGEs were linked with greater incidences of cardiovascular disease (CVD) [18]. Furthermore, AGEs increase the deposition of oxidized low-density lipoproteins (LDL) in vessels, reduce the concentration of nitric oxide, and enhance oxidative stress, leading to endothelial dysfunction [19]. Adiponectin is an adipocytokine that is involved in oxidative stress, and obesity-associated metabolic and cardiovascular disease pathogenesis. In agreement with this approach, the current study was designed to assess the possible benefit of ALA supplementation on advanced glycation end product (AGEs) serum levels in patients undertaking hemodialysis as a measure to assess endothelium function that correlates with CVEs. Also, we investigated the effects of ALA supplementation on serum adiponectin and lipid profile levels in HD patients [20].

Ethics approval

This study protocol was approved by the institutional ethical committee, which was in agreement with the Helsinki declaration, Code number: 419PP12. The clinical trial was registered in Clinical Trials.gov with

Code No: NCT03912727. A full study description was given for all patients, and a written agreement was gained from them prior to the study.

Method:

Patients and study design

A prospective, parallel, double-blind randomized clinical study conducted started in May 2019 and ended in August 2019. The effect of alpha-lipoic acid supplementation on serum levels of Hb (hemoglobin), serum Fe, ROS, lipid profile, and AGEs (advanced glycated end products) in chronic renal disease's patient undergoing HD was examined. This study was accomplished at the Nephrology Department, Dialysis units, Ain Shams University Hospitals, Ain Shams University, Cairo, Egypt.

Sample collection

Inclusion criteria: (1) Clinical stable patients on hemodialysis for at least 3 months. (2) Aged between 18 - 60 years old.3- Both sexes. (4) Patients who accept to participate in the study.

Exclusion criteria: (1) The patients suffering from any diseases, lead to oxidative stress, such as hepatic, respiratory or inflammatory diseases (2), Smokers and alcoholics. (3) Non-compliant patients. (4) History of using non-steroidal anti-inflammatory drugs, steroidal and vitamins C, E, and D also, valproate acid within 1 month previously the study, (5) gastric disorders, and (6) sensitivity or adverse reaction to ALA.

Out of 96 patients with ESRD undergoing HD, 78 were selected in this study based on inclusion criteria. The patient's baseline characteristics are documented in the data collection form. Additionally, the patient during their visit for dialysis was asked to fast for 12–14 hours on the subsequent visit. Withdrawal of 10 ml venous blood before starting dialysis was performed in a fasting state. These patients were randomly allocated into two groups: tested group received ALA (thiotacid® 600 mg tablet, a product of EVA Pharma, Cairo, Egypt) product and the second group who received a placebo with their standard therapy served as a control group (Fig. 1).

In order to have a double-blind study, both groups were given similar bottles of ALA capsules and placebo capsules. After 3 months, the blood samples were obtained from all patients having 12–14 h of fasting. Blood samples withdrawn from patients at the start and end of 3 months of interventions were reserved in the fridge -80 C°. Then, parameters were assessed according to the following method: AGEs level was estimated using a commercially available competitive enzyme-linked immunosorbent assay (ELISA) kits (Beijing Winter Song Boye Biotechnology Co Ltd., Beijing, China).

Serum levels of reactive oxygen species determined by enzyme-linked immunosorbent assay, (MyBioSource's co.). Blood hemoglobin was measured using BioVision's Hemoglobin Colorimetric Assay kit). Adiponectin levels were measured using ELISA (Enzyme-Linked Immunosorbent Assay) kits from RayBiotech Company, USA. Triglycerides (TGs), total cholesterol (TCH), and High-density lipoprotein (HDL-C) were determined colorimetry using kits obtained from Elitech Diagnostics Company, France. Low-density lipoprotein (LDL-C) was calculated using the Friedewald Equation: LDL-C=TCH-HDL-(TG/5)

Statistical analysis:

All data represented as mean ± SD, paired t-test was used. Correlation between measured variables was evaluated by Pearson's correlations. The statistical analysis was performed using IBM SPSS statistical package version 23.0 (SPSS Inc; USA, 2015). The level of significance was set at $P<0.05$.

RESULTS

70 ESRD patients undergoing hemodialysis were completed our study, 35 patients received ALA and 35 patients received a placebo (Fig.1). The starting point characteristics of these patients are presented in Table 1. No significant differences were found regarding gender, age, duration of dialysis, and causative factor for dialysis between the two groups ($P > 0.05$, Table 1). Table [2] showed: The mean serum levels of advanced glycation end products (AGEs), was highly reduced

after three months of treatment with of ALA in the tested group compared with their baseline, from 19.17±2.55 (ng/ml) to 9.67 ± 3.04 (ng/mL); agreeing to the independent t-test, this difference was statistically highly significant (P <0.001). On other hand in a control group, mean serum levels of AGEs was highly increased after 3 months compared with its baseline, from 18.94 ± 4.23 to 28.75 ± 6.73 (ng/ml); with significant differences (P <0.01), Figure 2; indicating that these patient`s group (control group) will be at high risk of CVEs. Our results from Table 2 showed that, the mean of Hb before and after the treatment in the tested group was 8.45±0.67and 11.45±1.62 (g/dL), respectively; this difference was highly statistically significant (P <0.001, Table.2). In the control group the mean level of Hb. before and after 3 months, it was 8.81±1.02 and decreased to 7.63±0.71, respectively; this difference was not statistically significant (P >0.05, Table.2). On the other hand, serum adiponectin level showed a significant increase after treatment with ALA for three months with a significant difference when compared to the control group.

Serum levels of Fe before and after ALA administration was 40.86±8.92and 62.77±19.61, respectively; this difference was statistically significant (P <0.05, Table.2). On the other hand, serum levels of Fe before and after the placebo administration was 44.17±5.90 and 39.77±6.21, respectively; this difference was not statistically significant statistically (P >0.05, Table.2).

Table [2] showed that the mean of reactive oxygen species (ROS) in the tested group was 7.55±1.16 ng/ml and this mean, after administration of ALA for 3 months, was highly reduced to 2.96±1.63 respectively; and its P-value was less than 0.05 (P=0.0001).

The mean of ROS before and after the placebo administration was 7.98±1.27 and 18.44±4.54, respectively; this difference was statistically significant (P <0.05).

Total cholesterol, LDL-C, and triglycerides levels, were insignificantly decreased upon treatment compared to control groups. On the other hand serum HDL-C level not changed in both groups.

Table [3]: showed a negative correlation between AGES after treatment with Hb and Fe levels (r= -0.73 and -0.39, P= 0.0001 and 0.01, respectively), Table 3. In contrast, a positive correlation was found between AGEs after treatment with ROS levels (r= 0.73, P= 0.0001). Also Hb after treatment revealed a positive correlation with Fe level (r= 0.39, P= 0.01), and a negative correlation with ROS level (r=-0.73, P= 0.0001). Fe level exhibited a negative correlation with ROS level (r=-0.37, P= 0.02).

Table [1] the baseline characteristics of patients on hemodialysis enrolled in the study

Parameter	Control group (n=35)	Tested group (n=35)	P value
Age (year)	**49.17±11.16**	**46.94±8.67**	**0.354**
Gender (n)			
Male	**18**	**19**	
Female	**17**	**16**	
Duration of dialysis (year)	**3.55±1.16**	**3.14±1.20**	**0.157**
Causative factor for dialysis (%)			
Diabetic	**16**	**17**	
Hypertension	**15**	**14**	
Glomerulonephritis	**8**	**7**	
Renal cystic diseases	**2**	**3**	

Control group: patients who receive their standard therapy only

Tested group: patients who receive alpha lipoic acid (thiotacid^{R}) product with their standard therapy.

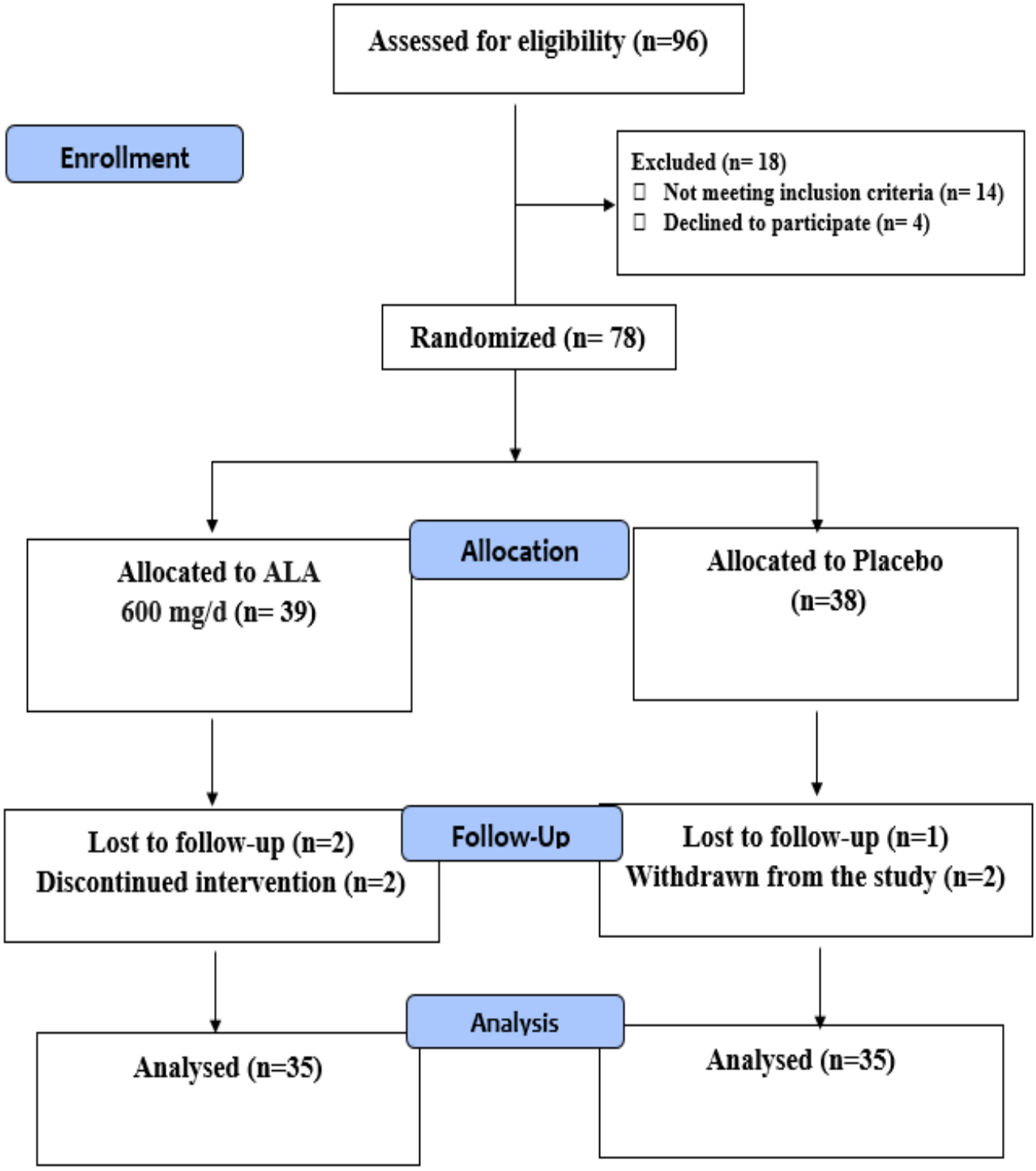

Figure 1: Flow Diagram of the progress through the parallel randomized study.

Table [2]: The measured biological markers of both groups before and after 3 months from starting the study.

Parameter	Control group (n=35)		Tested group (n=35)	
	At base line	**After 3 months**	**At base line**	**After 3 months**
BMI (kg/m^2)	**30.97**±2.06	30.53±2.04	**30.74**±2.94	30.45±2.86
AGEs (ng/ml)	**18.94±4.23**	28.75±6.73[b]	**19.17±2.55**	9.67±3.04 [a, c]
ROS (ng/ml)	7.98±1.27	18.44±4.54[b]	7.55±1.16	2.96±1.63 [a, c]
Hb (g/dL)	8.81±1.02	7.63±0.71	8.45±0.67	11.45±1.62 [a, c]
Fe (mcg/dL)	44.17±5.90	39.77±6.21[b]	40.86±8.92	62.77±19.61 [a]
TCH (mg/ml)	174.64±23.43	168.20±20.11	178.39±23.80	165.03±17.45
LDL-C (mg/ml)	112.47±24.19	107.49±20.10	116.07±24.19	104.21±17.58
HDL-C (mg/ml)	33.43±1.18	33.35±1.23	33.36±1.33	33.47±1.35
TG (mg/ml)	143.66±14.06	136.37±14.40	144.78±16.73	136.69±13.07
Adiponectin (pg/ml)	1.38±0.44	1.99±0.61	1.41±0.41	2.60±0.83[a,c]

AGE: advanced glycation end products; ROS: reactive oxygen species; Hb: serum levels of hemoglobin; Fe: serum level of iron; ROS: serum levels of reactive oxygen species.

[a]: significant P-value between tested group at base line and, after 3 months of study ($P < 0.05$), paired t test.

[b]: significant P-value between control group at base line and after 3 months. ($P < 0.05$)

[c]: significant P-value tested group and between control group after 3 months. ($P < 0.05$)

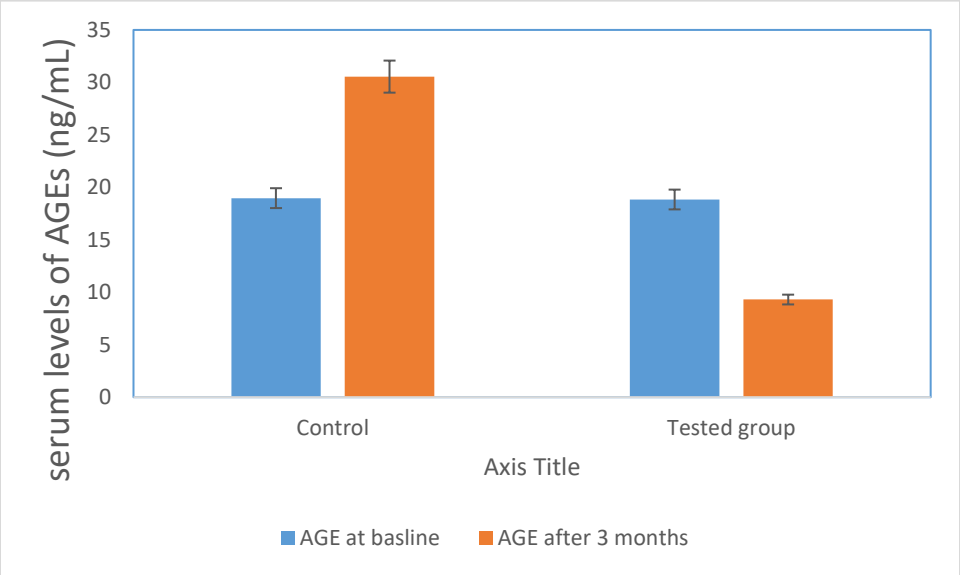

Figure [2] The mean serum levels of AGEs before and after 3 months of the intervention in control and tested group

Table [3]: Pearson Correlation between AGEs with measured parameters before and after three month of treatment in tested group.

	AGEs (r)
Adiponectin	-0.389**
TCH	0.230
LDL	0.175
HDL	0.072
TG	0.379**
ROS	0.778**
Hb	-0.621**
Fe	-0.538**

AGEs: serum level of Advanced Glycation End products; *ROS: serum level of Reactive Oxygen Species; Fe: iron; r: Pearson correlation*

**. Correlation is significant at the 0.01 level (2-tailed).

*. Correlation is significant at the 0.05 level (2-tailed).

Discussion

Our results revealed an increased level of serum AGEs in HD patients, therefore confirming previous reports**.** [21; 22] Because gathering of AGEs is supposed to have a role in the pathogenesis of aged, tissue, and age-related diseases such as type II diabetes. AGEs altitudes may consider as an indicator of tissue damage**.** [23] HD itself contributes to the development of endothelial dysfunction and CVD due to the numerous oxidative factors accumulation [24]. AGEs buildup may have a role in chronic transplant dysfunction, proposed by experimental and epidemiological information. However, interventions against AGEs accumulation in these patients have not yet been performed, our results demonstrate the administration of alpha-lipoic acid acts against AGEs accumulation leading to a significant reduction by about 50.44 % in serum levels of AGEs after three months of alpha-lipoic acid therapy for patients on hemodialysis, and so, predictable loss of endothelial dysfunction will be decreased, resulting in decline the cardiovascular events. AGEs constitute a molecule with an essential role in the pathophysiology of coronary heart disease [8]. The results of the present study validate highly decline in serum levels of ROS after 3 months of treatment with an alpha-lipoic acid by 41.42%. Thus approving earlier studies by of Himmelfarb J., et al., 2002, [24] and, Bayes B., et al., 2006 [25]**.** The growth of endothelial dysfunction is the first step in vascular calcification. Ghiadoni et al. studied the possible correlation between ROS, endothelial dysfunction and chronic kidney disease (CKD) severity in patients with CKD stage (3–5), the researchers discovered that endothelial dysfunction and ROS are strongly associated with advanced CKD. [26] The exact pathophysiologic mechanisms are up till now unclear even though, several researchers tried to explore the strong linkage between ROS and progression of atherosclerosis, the results from this study were observed that ROS was highly decreased in the hemodialyzed patients treated with alpha-lipoic acid, leading to decrease the chance of progression of atherosclerosis. [24] Thus development and advancement of atherosclerosis are tightly associated with ROS in CKD and HD patients. Our results found that after 3 months' treatment of lipoic acid, the serum levels of iron, and, hemoglobin were increased, at the same time, the serum levels of ROS, AGES were highly decreased. AGEs should be considered as major cardio-metabolic risk factors as it is directly associated with vascular stiffness and atherosclerosis as well as in modulation of intracellular signaling involved in endothelial cell response, and platelet activity [27]. Our results revealed that ALA supplementation resulted in a significant increase in serum adiponectin level in comparison with the placebo. The results of an animal study showed that ALA administration significantly enhanced adiponectin secretion in adipose tissue of rats fed with a high-fat diet [28]. The exact mechanisms of ALA effect on adiponectin secretion are not still known. However, it seems that oxidative stress and inflammation causes a reduction in the gene expression of adiponectin [29, 30]; and consequently, an antioxidant factors like ALA [31, 32] can increase adiponectin secretion from adipose tissue. This in agreement with a systematic review and meta-analysis of randomized controlled trials by Haghighatdoost et al., [33] which revealed that ALA increased adiponectin especially in studies with a follow-up duration for more than 8 weeks. The present study showed that ALA did not affect the lipid profile. Consistency with Mousavi et al., who showed that supplementation with ALA significantly decreased the serum concentrations of TG, total cholesterol, and low-density lipoprotein but did not affect serum levels of high-density lipoprotein in adults [34].

Inconsistence with a meta-analysis study concluded that ALA might favorably affect lipid profile especially LDL-C and TCH on the other hand; ALA did not reveal any significant change in serum triglyceride [35].

Conclusion

In summary, our study concludes that treatment with lipoic acid, increases the serum levels of adiponectin,

iron, and, hemoglobin, and did not affect lipid profiles among renal failure patients. On the other hand decrease the serum levels of ROS, AGEs and this can be directly implicated in vascular stiffness and atherosclerosis. So ALA can be beneficially recommended especially for renal and dialysis patients. Additional studies are needed with different ALA dose, duration, and separately on male and female.

Impact on practice statements: our findings could be applied in the clinic and hospital right away, they are likely to be of great interest to the vision of clinicians and health care professionals treating patients on hemodialysis.

Conflicts of Interest

The authors declared no potential conflicts of interest with respect to the research, authorship, and/or publication of this article.

Compliance with Ethical Standards:

This study was performed in agreement with the ethical standards of the institutional research committee and with the 1964 Helsinki declaration. Informed consent was obtained from all participants in the study.

Author Contributions

Hosny Ahmed Elewa, Zeinab Alkasaby Zalat, Walaa **A**. Keshk**,** and Rehab Hussein Werida contributed to conception, design, acquisition, analysis, writing, interpretation, and reviewing the manuscript.

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Data-Sharing Statement

Data will be shared on request by the corresponding author.

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