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# Alpha-lipoic acid improved anemia, erythropoietin resistance, maintained glycemic control, and reduced cardiovascular risk in diabetic patients on hemodialysis: a multi-center prospective randomized controlled study

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**Abstract. – OBJECTIVE: To investigate the impact of alpha-lipoic acid (ALA) on inflammation, oxidative stress, anemia, and glycemic parameters and their association with cardiovascular risk in diabetic patients on hemodialysis.**

**PATIENTS AND METHODS: In this multi-center, randomized, controlled study, 60 diabetic patients on hemodialysis were randomized into control group (n=30) which received Epoetin-alpha plus insulin therapy, and alpha-lipoic acid group (n=30) which received the same treatment plus alpha-lipoic acid (ALA) 600 mg once daily. Serum levels of high sensitivity C-reactive protein (hs-CRP), tumor necrosis factor-alpha (TNF-α), 8-hydroxy-2'-deoxyguanosine (8-OHdG), creatinine, urea, blood urea nitrogen (BUN), hemoglobin (Hb), iron parameters, fasting blood glucose (FBG), glycated hemoglobin (HbA1c), and fructosamine were measured at baseline and six months after intervention. The ankle-brachial index (ABI) was used to evaluate the clinical outcome. Erythropoietin resistance index (ERI), the weekly cost of Epoetin-alpha doses, and the total cost were calculated.**

**RESULTS: The two groups were statistically similar at baseline. After the intervention, as compared to the control group, ALA group showed significant reductions in serum levels of hs-CRP, TNF-α, 8-OHdG ($p$<0.001), urea, and BUN ($p$=0.029) with significant elevations in Hb concentration ($p$<0.001), serum iron ($p$=0.037) and transferrin saturation ($p$<0.001). ALA group showed a significant decline in FBG ($p$=0.004), HbA1c ($p$<0.001), fructosamine ($p$=0.005), ERI ($p$<0.001), weekly doses, and the weekly cost of Epoetin-alpha, and the total cost ($p$<0.001). ALA provided a cardio-protective effect, whereas the percentage of patients with acceptable ABI (0.9-1) was significantly higher in ALA group than in the control group ($p$=0.024), and those with abnormally low ABI (<0.9) were lower in the ALA group.**

**CONCLUSIONS: Due to its efficacy and safety, alpha-lipoic acid represents a pharmaco-economic supplement for diabetic patients on hemodialysis. Further trials are needed for complete evaluation of ALA effects.**

*Key Words:*
Alpha-lipoic acid, Hemodialysis, Hs-CRP, Anemia, Fructosamine, Erythropoietin resistance, Ankle-brachial index.

## Introduction

Diabetic patients who receive a constant and continuous hemodialysis (HD) are considered at a higher risk of morbidity and mortality as a consequence of inflammatory and oxidative stress disorders, which are correlated with chronic kidney and cardiovascular diseases[1,2]. Inflammatory cytokines were assumed to play a significant role in the development of anemia in patients with chronic renal failure through hypo-responsiveness to erythropoiesis-stimulating agents or erythropoietin resistance[3]. In this context, anemia management in patients with chronic kidney diseases becomes a challenging matter[4]. Furthermore, there is an association between the administration of large doses of erythropoietin and the increased risk of cardiovascular complications[5].

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Additionally, inflammatory cytokines and oxidative stress are usually associated with insulin resistance and subsequent glycemic control worsening in the diabetic population[6,7].

Glycated hemoglobin (HbA1c) is accredited in long-term follow-up of glycemic control and confirming the diagnosis of diabetes mellitus. Elevated HbA1c values are correlated with macro and microvascular complications, as well as increased cardiovascular mortality rates in diabetic patients on hemodialysis[8]. In patients on hemodialysis, HbA1c is influenced by chronic uremia, mechanical hemolysis, and hematopoiesis, which includes both iron status and erythropoietin-stimulating agents' dose[9]. Fructosamine and other non-traditional markers of hyperglycemia, including glycated albumin, are not affected by erythrocyte turnover, that may result from mechanical hemolysis, stimulated erythropoiesis, and bleeding[10]. Furthermore, fructosamine correlates with blood sugar levels, as does HbA1c, and it is considered a risk factor for cardiovascular events in dialysis patients[11].

Alpha-lipoic acid has been demonstrated to have anti-oxidant and anti-inflammatory activities[12]. ALA possesses a broad spectrum of metabolic benefits, including anti-obesity, insulin-sensitizing, and lipid-lowering effects[13]. These aforementioned properties focus the attention on the potential use of ALA in renal diseases, atherosclerosis, cardiovascular disease, and cardiovascular-related complications[14].

In this context, the current study aimed at investigating the impact of ALA on anemia, erythropoietin resistance, inflammation, oxidative stress, glycemic parameters (glycated hemoglobin, fructosamine) and evaluating their associated cardiovascular risk in diabetic patients on hemodialysis.

## Patients and Methods

### Study Design

The study design was a multi-center prospective, randomized, controlled study. The study was conducted between January 2020 and May 2021 at the outpatient dialysis unit of Urology and Nephrology Center, Alexandria Fever Hospital, and Borg El-Arab Hospital.

### Patient Population and Randomization

The stratified random block method was used to randomly assign 68 diabetic patients with end-stage renal disease on maintenance hemodialysis three times weekly into two groups in 1:1 ratio. The first group was the control group (group 1; n=34) which received a standard dose adjustment strategy of alpha recombinant human erythropoietin (Eposino®; United Pharma International Company, Cairo, Egypt) according to the KDOQI guidelines of 1997/2007 and insulin therapy. The second group was the alpha-lipoic acid group (group 2; n=34) which also received the same treatment as the control group, plus 600 mg of alpha-lipoic acid (Thiotex Forte®; capsules, Marcyrl Pharmaceutical Industries, Egypt) once daily; during the days of hemodialysis, the dose was scheduled to be after the hemodialysis session. The study duration was six months.

### Inclusion Criteria

The inclusion criteria were patients of both sexes, age > 30 and < 70 years old. Diabetic patients with end-stage renal disease on maintenance hemodialysis three times weekly, their hemoglobin levels were between 8-10 g/dl, and were treated with standard-dose adjustment strategies of Epoetin alpha according to the KDOQI guidelines of 1997/2007 (4000-12000 U/dose) and insulin therapy.

### Exclusion Criteria

Patients with symptoms of active infection, active inflammation, malignancies, those receiving chemotherapy, active hepatitis C and B, history of recent surgery or significant blood loss, acute gastrointestinal bleedings, hemoglobinopathies (thalassemia), and pregnant women were all excluded.

### Ethical Approval

Tanta University's Ethics Committee approved the study protocol (Approval code: 33389/10/19), which was accepted and approved by the Ethics Committee of Alexandria Fever Hospital and Borg El-Arab Hospital. The study was carried out in accordance with the ethical guidelines of the Helsinki Declaration of 1975. All participants and their representatives provided their written informed consents.

### Demography, Medical History, and Anthropometric Measurements

All participants were subjected to demographics (age, sex, medication history, smoking habits, and numbers of years on dialysis), physical examination, weight and height measurement, with subsequent calculation of body mass index

(BMI). The patients' weights and height were measured at baseline and after intervention in the dialysis unit after dialysis session using Detecto Scale (Detecto Company, Missouri, MO, USA). Body mass index (BMI) was calculated by dividing weight (kilograms) by the square of height (meters) i.e., BMI = [weight (kg)] ÷ [height ($m^2$)].

### Collection and Measurement of Blood Samples

Blood samples were collected to measure study parameters during appointments scheduled by the dialysis unit for routine patients' examinations before and after the intervention. After overnight fasting, 10 ml of venous blood was withdrawn from each patient by antecubital venipuncture. 2 ml of blood sample was used to determine hemoglobin concentration by Automated Hematology Analyzer (Sysmex®XN-1000TM; Code: 19732, Japan). Another 2 ml of blood was transferred into Ethylenediaminetetraacetic acid (EDTA) test tubes to measure the percentage of HbA1c, assayed through the ion-exchange chromatographic spectrometric method using the glycated hemoglobin reagent kit (Biosystems reagents and instruments, Costa Brava, Spain). The remaining 6 ml of blood was transferred into plain test tubes and centrifuged at 4500×g for 10 min. The separated serum was divided into two portions. The first portion of serum was frozen at -80ºC until biochemical analysis of high sensitivity C-reactive protein (hs-CRP), tumor necrosis factor-alpha (TNF-α), 8-hydroxy-2'- deoxyguanosine (8-OHdG), and ferritin. The commercially available enzyme-linked immunosorbent assay (ELISA) kits were used to assay hs-CRP, TNF-α, and 8-OHdG levels (SunRed Biological Technology Company, Shanghai, China; Catalogue No.: 201-12-1806; 201-12-0083 and 201-12-1437, respectively). Serum ferritin level was assayed by ELISA technique (MyBio-Source, Inc., USA. Catalog No.: MBS843444). The second portion of serum was used for instant determination of fasting blood glucose (glucose oxidase method, Bio-Diagnostic, Egypt, catalogue No.: GL1320), fructosamine (colorimetric method, Spinreact, Spain, catalogue No.: 1001158), serum creatinine (colorimetric method with deproteinization, Bio-Med Diagnostics, Egypt, catalogue No.: CRE105120), urea and blood urea nitrogen (enzymatic colorimetric method; Bio-Med Diagnostics, Egypt, catalogue No.: URE118120), serum iron (colorimetric method, Bio-Diagnostic, Egypt, catalogue No.: IR1510) and total iron-binding capacity (TIBC) (saturation/precipitation method, Bio-Diagnostic, Egypt, catalogue No.: TI 1511). Transferrin saturation (TSAT %) was calculated by dividing the serum iron concentration by the total iron-binding capacity and multiplying the result by 100 to obtain a percentage. Glycated hemoglobin was assayed at baseline and every three months, while blood glucose and fructosamine levels were assayed every month.

### Calculation of Erythropoietin Resistance Index

Erythropoietin resistance index (ERI) is defined as average weekly erythropoietin (EPO) dose per kg body weight (wt) per average hemoglobin (Hgb): ERI = [(EPO/wt)/Hgb)] in IU/kg/week/g/dl[15].

### Assessment of the Clinical Outcomes

The clinical outcomes were assessed using the Ankle-brachial index (ABI) which has been reported to be independently associated with all causes of mortality including cardiovascular disease-related mortality in patients on hemodialysis. It has the potential to screen for coronary artery disease as a quick, non-invasive test for peripheral artery disease[16,17]. The ankle-brachial index was measured by Sonoline Pocket Doppler (Sonoloine B Model). The ankle-brachial index can be calculated by dividing the systolic blood pressure at the ankle by the systolic blood pressure in the arm "Ankle SP/arm SP"[18].

### Assessment of Participants' Adherence and Drug Tolerability

The participants' adherence was measured by counting the returned empty strips of alpha-lipoic acid capsules which were distributed at monthly intervals. Participants were also followed-up during their dialysis sessions to evaluate their adherence and report any drug-related adverse effects using an adverse effect reporting form. The patient was considered non-adherent if consumed less than the provided capsules. Non-adherent patients and those lost to follow-up were excluded from the study, and their preliminary data were excluded from the final analysis.

### Pharmacoeconomic Analysis

The weekly doses of alpha recombinant human erythropoietin and the total weekly cost (iron, alpha recombinant human erythropoietin, insulin, and alpha-lipoic acid capsules) were calculated at baseline and by the end of the intervention.

### Statistical Analysis

Statistical analyses were conducted with the IBM SPSS software package version 20.0. (IBM, Armonk, NY, USA). The Kolmogorov-Smirnov test was used to verify the normality of the data distribution. The two groups were statistically compared using unpaired *t*-test or Mann-Whitney tests for parametric or non-parametric data, respectively. Measurements within the same group were statistically compared using paired *t*-test or Wilcoxon signed-ranks test for parametric or non-parametric data, respectively. The Chi-square test or Fisher's exact test was used to compare different groups for categorical variables. Qualitative data were presented as numbers and percentages. Quantitative data were presented as range and mean± SD. The level of significance was set at $p<0.05$.

## Results

Thirty-six patients were excluded from the total of 104 patients enrolled (24 patients did not meet the inclusion criteria and 12 patients declined to participate). Therefore, 68 patients were randomized into the two study groups. A total of 8 patients were dropped out during the follow-up period (4 patients in each group) secondary to death, change of dialysis center, non-adherence to study medication, and missed data, and their preliminary data were excluded from the final analysis, which included 30 patients in each arm. Participants' screening, randomization, and follow-up are depicted in Figure 1.

### Baseline Data

At baseline, the two groups were statistically similar with respect to age, sex ratio, height, smoking habit, number of years on dialysis, and medical history ($p>0.05$), as shown in Table I.

At baseline, the two groups were statistically similar ($p>0.05$) in terms of weight, body mass index (BMI), dialysis adequacy, measured laboratory parameters including inflammatory markers (hs-CRP, TNF-α), oxidative stress marker (8-OHdG), renal function (serum creatinine, urea and BUN), hemoglobin concentration, serum

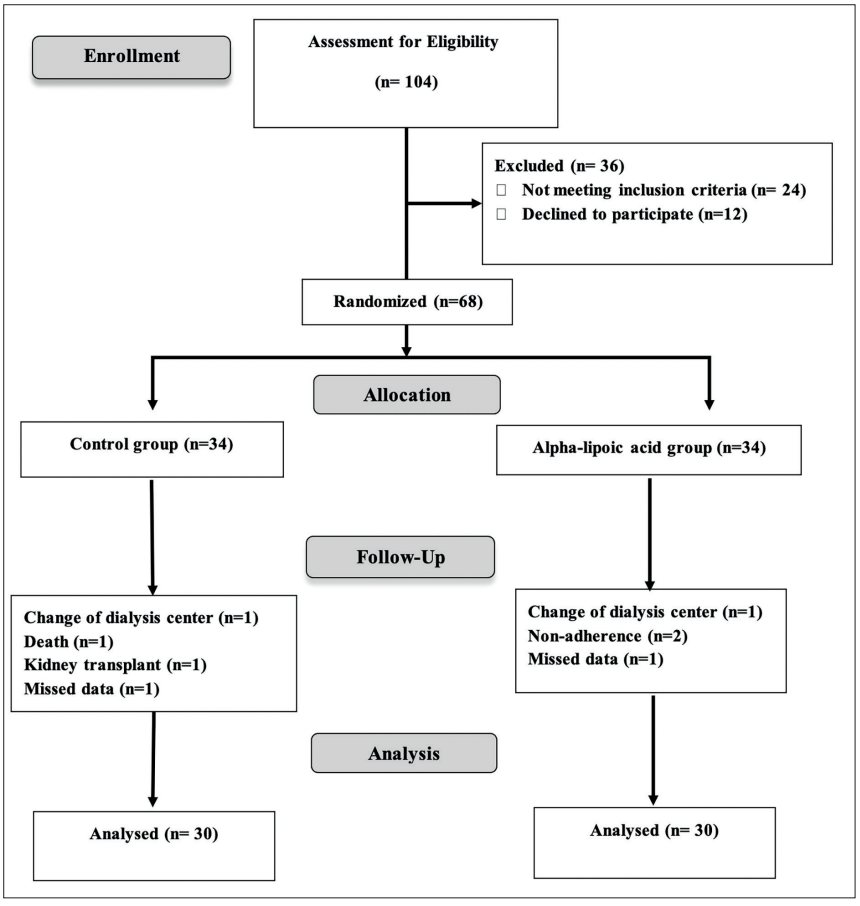


**Figure 1.** Participants' flow-chart.

**Table I.** Baseline demographic and medical history of the study participants.

| Parameters | Control group (n = 30) | | Alpha-lipoic acid (n = 30) | | *p*-value |
|---|---|---|---|---|---|
| | Mean ± SD | | Mean ± SD | | |
| **Age (years)** | 46.03 ± 4.92 | | 44.43 ± 7.03 | | 0.312 |
| | **N** | **%** | **N** | **%** | |
| **Gender** | | | | | 0.602 |
| Male | 14 | 46.7 | 12 | 40 | |
| Female | 16 | 53.3 | 18 | 60 | |
| **Height (cm)** | 167.2 ± 6.87 | | 166.9 ± 7.51 | | 0.872 |
| | **N** | **%** | **N** | **%** | |
| Smokers | | | | | 0.584 |
| No | 19 | 63.3 | 21 | 70 | |
| Yes | 11 | 36.7 | 9 | 30 | |
| **Years on dialysis** | 4.77 ± 1.38 | | 5.07 ± 1.28 | | 0.387 |
| **Other comorbidity** | **N** | **%** | **N** | **%** | |
| **Asthma** | | | | | 0.592 |
| No | 20 | 66.7 | 18 | 60 | |
| Yes | 10 | 33.3 | 12 | 40 | |
| **Migraine** | | | | | 0.584 |
| No | 15 | 50 | 19 | 63.3 | |
| Yes | 15 | 50 | 11 | 36.7 | |

Data are presented as mean ± SD, number (N) and percent (%). Cm: centimeter. Significance level was set at $p < 0.05$.

iron, total iron-binding capacity (TIBC), transferrin saturation (TSAT), serum ferritin, doses of iron/month, doses of erythropoietin stimulating agent (ESA)/week, erythropoietin resistance index (ERI), glycemic parameters (fasting blood glucose "FBG", glycated hemoglobin "HbA1c", fructosamine), daily doses of insulin, ankle-brachial index (ABI), cost of ESA doses/week (LE) and total cost/week (ESA+ iron+ insulin +ALA), as demonstrated in Table II.

### Effect of the Intervention on Anthropometric Parameters

The control group showed non-significant differences in body weight (70.57 ± 9.74 kg *vs.* 69.53 ± 8.92 kg; $p$=0.160) and body mass index (25.25 ± 3.14 kg/m$^2$ *vs.* 24.87 ± 2.62 kg/m$^2$; $p$=0.174) 6 months after intervention compared to baseline data. Also, the alpha-lipoic acid group showed non-significant changes in body weight and body mass index (69.40 ± 9.10 kg *vs.* 69.46 ± 9.02 kg; $p$=0.495 and 24.92 ± 2.74 kg/m$^2$ *vs.* 24.94 ± 2.70 kg/m$^2$; $p$=0.549, respectively), as illustrated in Table III.

Post-intervention comparisons between the two study groups revealed non-significant differences between the two study groups regarding body weight and body mass index (69.53 ± 8.92 kg *vs.* 69.46 ± 9.02 kg; $p$=0.975 and 24.87 ± 2.62 kg/m$^2$ *vs.* 24.94 ± 2.70 kg/m$^2$; $p$=0.913, respectively), as shown in Table IV.

### Effect of the Intervention on Inflammatory and Oxidative Stress Biomarkers

The control group showed non-significant differences in serum levels of hs-CRP (14.59 ± 3.25 mg/L *vs.* 14.98 ± 3.84 mg/L; $p$=0.161), TNF-α (18.27 ± 5.69 ng/L *vs.* 18.11 ± 6.01 ng/L; $p$=0.505) and 8-OHdG (4.94 ± 1.01 ng/ml *vs.* 4.70 ± 0.81 ng/ml; $p$=0.058) 6 months after the intervention compared to baseline data. In contrast, alpha-lipoic acid group demonstrated a significant decline in the serum levels of hs-CRP (15.17 ± 3.18 mg/L *vs.* 11.14 ± 2.36 mg/L; $p$<0.001), TNF-α (17.43 ± 4.32 ng/L *vs.* 11.44 ± 3.28 ng/L; $p$<0.001) and 8-OHdG (5.02 ± 0.87 ng/ml *vs.* 2.95 ± 0.79 ng/ml; $p$<0.001), as postulated in Table III.

**Table II.** Baseline anthropometric and laboratory data of the study participants.

| Parameters | Control group (n = 30) Mean ± SD | Alpha-lipoic acid (n = 30) Mean ± SD | *p*-value |
|---|---|---|---|
| Weight (kg) | 70.57 ± 9.74 | 69.40 ± 9.10 | 0.633 |
| BMI (kg/m$^2$) | 25.25 ± 3.14 | 24.92 ± 2.74 | 0.670 |
| Kt/V | 1.32 ± 0.07 | 1.30 ± 0.07 | 0.371 |
| hs-CRP (mg/L) | 14.59 ± 3.25 | 15.17 ± 3.18 | 0.492 |
| TNF-α (ng/L) | 18.27 ± 5.69 | 17.43 ± 4.32 | 0.521 |
| 8-OHdG (ng/ml) | 4.94 ± 1.01 | 5.02 ± 0.87 | 0.744 |
| S.Cr (mg/dl) | 8.43 ± 2.54 | 9.03 ± 2.48 | 0.383 |
| Urea (mg/dl) | 131.1 ± 24.17 | 124.6 ± 24.82 | 0.311 |
| BUN (mg/dl) | 61.17 ± 11.28 | 58.15 ± 11.58 | 0.311 |
| Hb (g/dl) | 8.99 ± 0.68 | 9.13 ± 0.70 | 0.466 |
| Serum iron (µg/dl) | 59.8 ± 33.94 | 59.63 ± 27.59 | 0.983 |
| TIBC (µg/dl) | 168.0 ± 100.5 | 171.3 ± 76.58 | 0.501 |
| TSAT (%) | 36.19 ± 3.74 | 34.65 ± 2.66 | 0.072 |
| Ferritin (ng/ml) | 503.5 ± 350.3 | 474.2 ± 277.6 | 0.745 |
| Doses of iron/month (mg) | 310.0 ± 158.3 | 353.3 ± 171.7 | 0.628 |
| Doses of ESA/week ( IU) | 15410.0 ± 5481.3 | 14827.0 ± 6248.9 | 0.464 |
| ERI (IU/kg/week/g/dl) | 25.15 ± 10.28 | 24.02 ± 10.53 | 0.378 |
| FBG (mg/dl) | 171.6 ± 33.28 | 168.7 ± 21.12 | 0.685 |
| HbA1c (%) | 8.40 ± 2.06 | 8.52 ± 1.35 | 0.796 |
| Fructosamine (µmol/L) | 569.0 ± 186.5 | 568.7 ± 136.8 | 0.994 |
| Daily doses of insulin (IU) | 55.67 ± 17.41 | 61.83 ± 13.23 | 0.128 |
| Ankle Brachial Index (ABI) | 1.01 ± 0.10 | 1.06 ± 0.13 | 0.115 |
| Cost of ESA doses/week (LE) | 208.0 ± 74.0 | 200.2 ± 84.36 | 0.464 |
| Total cost/week (ESA + iron + Insulin +ALA) | 248.1 ± 75.58 | 264.2 ± 89.87 | 0.456 |

Data are presented as mean ± SD. Kg: kilogram; m$^2$: meter square; Kt/V: dialysis adequacy where K = dialyzer clearance of urea, *t* = dialysis time, V = volume of distribution of urea; hs-CRP: Highly sensitive C-reactive protein; TNF-α: Tumor necrosis factor–alpha; 8-OHdG: 8-hydroxy-2'- deoxyguanosine; S.Cr: Serum Creatinine; BUN: Blood urea nitrogen; Hb: Hemoglobin; TIBC: Total iron binding capacity; TSAT: Transferrin saturation; ESA: Erythropoiesis stimulating Agents; IU: international units; ERI: Erythropoietin resistance index; FBG: fasting blood glucose; HbA1c: glycated hemoglobin; ALA: Alpha-lipoic acid. Significance level was set at $p < 0.05$.

Post-intervention comparisons between the two study groups revealed that the alpha-lipoic acid group provoked a significant reduction in the serum levels of hs-CRP (14.98 ± 3.84 mg/L *vs.* 11.14 ± 2.36 mg/L; $p<0.001$), TNF-α (18.11 ± 6.01 ng/L *vs.* 11.44 ± 3.28 ng/L; $p<0.001$), and 8-OHdG (4.70 ± 0.81 ng/ml *vs.* 2.95 ± 0.79 ng/ml; $p<0.001$) as compared to the control group. The comparison between the two study groups after the intervention is demonstrated in Table IV.

### *Effect of the Intervention on Dialysis Adequacy Kidney Function Related Parameters*

The control group showed non-significant differences in dialysis adequacy "Kt/v" (1.32 ± 0.07 *vs.* 1.33 ± 0.05; $p=0.510$) 6 months after intervention compared to baseline data. The control group demonstrated a significant decline in the serum creatinine level (8.43 ± 2.54 mg/dl *vs.* 6.49 ± 2.64 mg/dl; $p=0.019$) with non-significant difference in serum urea and blood urea nitrogen "BUN" levels (131.1 ± 24.17 mg/dl *vs.* 130.0 ± 22.49 mg/dl; $p=0.670$ and 61.17± 11.28 mg/dl *vs.* 60.67± 10.50 mg/dl; $p=0.670$, respectively). On the other hand, alpha-lipoic acid group showed non-significant difference in Kt/v (1.30 ± 0.07 *vs.* 1.31 ± 0.06; $p=0.822$) and significant decline in the serum creatinine (9.03 ± 2.48 mg/dl *vs.* 5.07 ± 1.54 mg/dl; $p<0.001$), urea (124.6 ±24.82 mg/dl *vs.* 116.1± 25.52 mg/dl; $p<0.001$) and BUN (58.15± 11.58 mg/dl *vs.* 54.16± 11.91 mg/dl; $p<0.001$), as postulated in Table III.

Post-intervention comparisons revealed that the two groups were statistically similar in terms of dialysis adequacy (1.33 ± 0.05 *vs.* 1.31 ± 0.06; $p=0.112$). When compared to the control group, the ALA group demonstrated significant reduction in the serum urea (130.0 ± 22.49 mg/dl *vs.* 116.1 ± 25.52 mg/dl; $p= 0.029$) and BUN (60.67 ± 10.50 mg/dl *vs.* 54.16 ± 11.91 mg/dl;

**Table III.** Anthropometric and laboratory data of the two study groups at baseline and after intervention.

| Parameters | Control group (n = 30) | | | Alpha-lipoic acid (n = 30) | | |
|---|---|---|---|---|---|---|
| | Baseline Mean ± SD | After treatment Mean ± SD | *p*-value | Baseline Mean ± SD | After treatment Mean ± SD | *p*-value |
| Weight (kg) | 70.57 ± 9.74 | 69.53 ± 8.92 | 0.160 | 69.40 ± 9.10 | 69.46 ± 9.02 | 0.495 |
| BMI (kg/m$^2$) | 25.25 ± 3.14 | 24.87 ± 2.62 | 0.174 | 24.92 ± 2.74 | 24.94 ± 2.70 | 0.549 |
| Kt/V | 1.32 ± 0.07 | 1.33 ± 0.05 | 0.510 | 1.30 ± 0.07 | 1.31 ± 0.06 | 0.822 |
| hs-CRP (mg/L) | 14.59 ± 3.25 | 14.98 ± 3.84 | 0.161 | 15.17 ± 3.18 | 11.14 ± 2.36 | < 0.001 |
| TNF-α (ng/L) | 18.27 ± 5.69 | 18.11 ± 6.01 | 0.505 | 17.43 ± 4.32 | 11.44 ± 3.28 | < 0.001 |
| 8-OHdG(ng/ml) | 4.94 ± 1.01 | 4.70 ± 0.81 | 0.058 | 5.02 ± 0.87 | 2.95 ± 0.79 | < 0.001 |
| S.Cr (mg/dl) | 8.43 ± 2.54 | 6.49 ± 2.64 | 0.019 | 9.03 ± 2.48 | 5.07 ± 1.54 | <0.001 |
| Urea (mg/dl) | 131.1 ± 24.17 | 130.0 ± 22.49 | 0.670 | 124.6 ± 24.82 | 116.1 ± 25.52 | <0.001 |
| BUN (mg/dl) | 61.17 ± 11.28 | 60.67 ± 10.50 | 0.670 | 58.15 ± 11.58 | 54.16 ± 11.91 | <0.001 |
| Hb (g/dl) | 8.99 ± 0.68 | 9.28 ± 0.96 | 0.135 | 9.13 ± 0.70 | 10.57 ± 0.69 | <0.001 |
| Serum iron (µg/dl) | 59.8 ± 33.94 | 55.53 ± 35.65 | 0.432 | 59.63 ± 27.59 | 71.97 ± 22.29 | 0.021 |
| TIBC (µg/dl) | 168.0 ± 100.5 | 241.6 ± 170.8 | 0.018 | 171.3 ± 76.58 | 199.6 ± 68.81 | 0.016 |
| TSAT (%) | 36.19 ± 3.74 | 25.99 ± 8.52 | < 0.001 | 34.65 ± 2.66 | 37.09 ± 6.16 | 0.056 |
| Ferritin (ng/ml) | 503.5 ± 350.3 | 427.8 ± 267.2 | 0.075 | 474.2 ± 277.6 | 364.6 ± 163.3 | 0.022 |
| Monthly doses of iron (mg) | 310.0 ± 158.3 | 500.0 ± 353.3 | 0.009 | 353.3 ± 171.7 | 206.7 ± 86.83 | < 0.001 |
| Doses of ESA/week ( IU) | 15410 ± 5481.3 | 15057.5 ± 6233.3 | 0.741 | 14827.0 ± 6248.9 | 7345.4 ± 4413.3 | < 0.001 |
| ERI (IU/kg/week/g/dl) | 25.15 ± 10.28 | 24.56 ± 11.56 | 0.375 | 24.02 ± 10.53 | 10.35 ± 7.30 | < 0.001 |
| FBG (mg/dl) | 171.6 ± 33.28 | 169.5 ± 24.16 | 0.615 | 168.7 ± 21.12 | 150.3 ± 25.70 | 0.001 |
| HbA1c (%) | 8.40 ± 2.06 | 8.47 ± 1.63 | 0.830 | 8.52 ± 1.35 | 7.11 ± 1.20 | < 0.001 |
| Fructosamine (µmol/L) | 569.0 ± 186.5 | 559.3 ± 154.9 | 0.756 | 568.7 ± 136.8 | 437.3 ± 168.1 | < 0.001 |
| Daily doses of insulin (IU) | 55.67 ± 17.41 | 56.53 ± 16.53 | 0.636 | 61.83 ± 13.23 | 49.23 ± 11.08 | < 0.001 |
| ABI | 1.01 ± 0.10 | 1.0 ± 0.18 | 0.825 | 1.06 ± 0.13 | 0.94 ± 0.04 | < 0.001 |
| Cost of ESA doses/week (LE) | 208.0 ± 74.0 | 203.3 ± 84.15 | 0.741 | 200.2 ± 84.36 | 99.16 ± 59.58 | < 0.001 |
| Total cost/week (ESA + iron + insulin +ALA) | 248.1 ± 75.58 | 255.0 ± 96.64 | 0.738 | 264.2 ± 89.87 | 149.5 ± 61.88 | < 0.001 |

Data are presented as mean ± SD. Kg: kilogram; m$^2$: meter square; Kt/V: dialysis adequacy where K = dialyzer clearance of urea, *t* = dialysis time, V = volume of distribution of urea; hs-CRP: Highly sensitive C-reactive protein; TNF-α: Tumor necrosis factor–alpha; 8-OHdG: 8-hydroxy-2'-deoxyguanosine; S.Cr: Serum Creatinine; BUN: Blood urea nitrogen; Hb: Hemoglobin; TIBC: Total iron binding capacity; TSAT: Transferrin saturation; ESA: Erythropoiesis stimulating Agents; IU: international units; ERI: Erythropoietin resistance index; FBG: fasting blood glucose; HbA1c: glycated hemoglobin; ABI: Ankle Brachial Index; ALA: Alpha-lipoic acid. Significance level was set at $p < 0.05$.

*p*= 0.029) without significant variation in the serum creatinine levels between the two study groups (6.49 ± 2.64 mg/dl *vs.* 5.07± 1.54 mg/dl; *p*=0.063). The comparison between the two study groups after the intervention is demonstrated in Table IV.

### *Effect of Intervention on Anemia, Iron Indices, and Erythropoietin Resistance*

The control group showed non-significant differences in hemoglobin level (8.99 ± 0.68 g/dl *vs.* 9.28 ± 0.96 g/dl; *p*=0.135), serum iron level (59.8 ± 33.94 µg/dl *vs.* 55.53 ± 35.65 µg/dl; *p*=0.432) and serum ferritin level (503.5 ± 350.3 ng/ml *vs.* 427.8 ± 267.2 ng/ml; *p*=0.075) with a significant decline in transferrin saturation "TSAT" (36.19± 3.74 % *vs.* 25.99± 8.52 %; *p*<0.001) and a significant increase in TIBC (168.0 ± 100.5 µg/dl *vs.* 241.6 ± 170.8 µg/dl; *p*=0.018) six months after intervention compared to baseline data. Furthermore, the control group demonstrated a significant increase in monthly iron doses (310.0 ± 158.3 mg *vs.* 500.0 ±353.3 mg; *p*=0.009) with non-significant differences in weekly doses of alpha recombinant human erythropoietin (15410.0 ± 5481.3 IU *vs.* 15057.5 ± 6233.3 IU; *p*=0.741) and erythropoietin resistance index "ERI" (25.15 ± 10.28 *vs.* 24.56 ± 11.56; *p*=0.375). Alpha-lipoic acid group showed significant elevation in hemoglobin level (9.13 ± 0.70 g/dl *vs.* 10.57 ± 0.69 g/dl; *p*<0.001), serum iron level (59.63 ± 27.59 µg/dl *vs.* 71.97 ± 22.29 µg/dl; *p*=0.021), TIBC (171.3 ± 76.58 µg/dl *vs.* 199.6 ± 68.81 µg/dl; *p*=0.016) and a significant decline in serum ferritin (474.2 ± 277.6 ng/ml *vs.* 364.6 ± 163.3 ng/ml; *p*=0.022) with no significant change in TSAT (34.65 ± 2.66

**Table IV.** The comparison between the two study groups after intervention.

| Parameters | Control group (n = 30) Mean ± SD | Alpha-lipoic acid (n = 30) Mean ± SD | *p*-value |
|---|---|---|---|
| Weight (kg) | 69.53 ± 8.92 | 69.46 ± 9.02 | 0.975 |
| BMI (kg/m$^2$) | 24.87 ± 2.62 | 24.94 ± 2.70 | 0.913 |
| Kt/V | 1.33 ± 0.05 | 1.31 ± 0.06 | 0.112 |
| hs-CRP (mg/L) | 14.98 ± 3.84 | 11.14 ± 2.36 | < 0.001 |
| TNF-α (ng/L) | 18.11 ± 6.01 | 11.44 ± 3.28 | < 0.001 |
| 8-OHdG (ng/ml) | 4.70 ± 0.81 | 2.95 ± 0.79 | < 0.001 |
| S. Cr (mg/dl) | 6.49 ± 2.64 | 5.07 ± 1.54 | 0.063 |
| Urea (mg/dl) | 130.0 ± 22.49 | 116.1 ± 25.52 | 0.029 |
| BUN (mg/dl) | 60.67 ± 10.50 | 54.16 ± 11.91 | 0.029 |
| Hb (g/dl) | 9.28 ± 0.96 | 10.57 ± 0.69 | < 0.001 |
| Serum iron (µg/dl) | 55.53 ± 35.65 | 71.97 ± 22.29 | 0.037 |
| TIBC (µg/dl) | 241.6 ± 170.8 | 199.6 ± 68.81 | 0.935 |
| TSAT (%) | 25.99 ± 8.52 | 37.09 ± 6.16 | < 0.001 |
| Ferritin (ng/ml) | 427.8 ± 267.2 | 364.6 ± 163.3 | 0.284 |
| Monthly doses of iron (mg) | 500.0 ± 353.3 | 206.7 ± 86.83 | < 0.001 |
| Weekly doses of ESA (IU) | 15057.5 ± 6233.3 | 7345.4 ± 4413.3 | < 0.001 |
| ERI (IU/kg/week/g/dl) | 24.56 ± 11.56 | 10.35 ± 7.30 | < 0.001 |
| FBG (mg/dl) | 169.5 ± 24.16 | 150.3 ± 25.70 | 0.004 |
| HbA1c (%) | 8.47 ± 1.63 | 7.11 ± 1.20 | < 0.001 |
| Fructosamine (µmol/L) | 559.3 ± 154.9 | 437.3 ± 168.1 | 0.005 |
| Daily doses of insulin (IU) | 56.53 ± 16.53 | 49.23 ± 11.08 | 0.049 |
| Ankle Brachial Index (ABI) | 1.0 ± 0.18 | 0.94 ± 0.04 | 0.045 |
| Cost of ESA doses/week (LE) | 203.3 ± 84.15 | 99.16 ± 59.58 | < 0.001 |
| Total cost/week (LE) (ESA + iron+ Insulin +ALA) | 255.0 ± 96.64 | 149.5 ± 61.88 | < 0.001 |

Data are presented as mean ± SD. Kg: kilogram; m$^2$: meter square; Kt/V: dialysis adequacy where K = dialyzer clearance of urea, *t* = dialysis time, V = volume of distribution of urea; hs-CRP: Highly sensitive C-reactive protein; TNF-α: Tumor necrosis factor-alpha; 8-OHdG: 8-hydroxy-2'- deoxyguanosine; S.Cr: Serum Creatinine; BUN: Blood urea nitrogen; Hb: Hemoglobin; TIBC: Total iron binding capacity; TSAT: Transferrin saturation; ESA: Erythropoiesis stimulating Agents; IU: international units; ERI: Erythropoietin resistance index; FBG: fasting blood glucose; HbA1c: glycated hemoglobin; ALA: Alpha-lipoic acid. Significance level was set at $p < 0.05$.

% *vs.* 37.09 ± 6.16 %; $p$=0.056). Furthermore, alpha-lipoic acid group showed a significant decline in monthly iron doses (353.3 ± 171.7 mg *vs.* 206.7±86.83 mg; $p$<0.001), weekly doses of alpha recombinant human erythropoietin (14827.0 ± 6248.9 IU *vs.* 7345.4 ± 4413.3 IU; $p$<0.001) and erythropoietin resistance index "ERI" (24.02 ± 10.53 *vs.* 10.35 ± 7.30; $p$<0.001), as postulated in Table III.

The comparison of the two study groups after intervention revealed that, when compared to the control group, the ALA group demonstrated a significant increase in hemoglobin concentration (9.28 ± 0.96 g/dl *vs.* 10.57 ± 0.69 g/dl; $p$<0.001), serum iron level (55.53 ± 35.65 µg/dl *vs.* 71.97 ± 22.29 µg/dl; $p$=0.037), TSAT (25.99 ± 8.52 % *vs.* 37.09 ± 6.16 %; $p$<0.001) with no significant difference in the serum ferritin level (427.8 ± 267.2 ng/ml *vs.* 364.6 ± 163.3 ng/ml; $p$=0.284) and TIBC (241.6 ± 170.8 µg/dl *vs.* 199.6 ± 68.81 µg/dl; $p$=0.935). As compared to the control group, the ALA group showed significantly decreased monthly doses of iron and weekly doses of alpha recombinant human erythropoietin (500.0 ± 353.3 mg *vs.* 206.7 ± 86.83 mg; $p$<0.001 and 15057.5 ± 6233.3 IU *vs.* 7345.4 ± 4413.3 IU; $p$<0.001). Additionally, the alpha-lipoic acid group showed a significantly improved erythropoietin resistance index than the control group (24.56 ± 11.56 *vs.* 10.35 ± 7.30; $p$<0.001). The comparison between the two study groups after the intervention is demonstrated in Table IV.

### *Effect of Intervention on Glycemic Parameters*

During the course of the study, the control groups showed significant reduction in FBG and fructosamine level compared to baseline data at the third, fourth and fifth months (171.6 ± 33.28 mg/dl *vs.* 145.3 ± 14.41 mg/dl; $p$<0.001: 171.6 ± 33.28 mg/dl *vs.* 144.6 ± 13.18 mg/dl; $p$=0.013, 171.6 ± 33.28 mg/dl *vs.* 140.0 ± 17.71

mg/dl; $p$=0.006, respectively for FBG and 569.0± 186.5 µmol/L *vs.* 425.3 ± 105.2 µmol/L; $p$<0.001: 569.0 ± 186.5 µmol/L *vs.* 418.2 ± 94.62 µmol/L; $p$=0.029, 569.0 ± 186.5 µmol/L *vs.* 371.7± 122.8 µmol/L; $p$=0.004, respectively for fructosamine). However, compared to baseline data, the control group demonstrated significant elevation of HbA1c at the third month of the study (8.40 ± 2.06 % *vs.* 9.35 ± 1.26 %; $p$=0.041) without significant difference between baseline and six months data (8.40 ± 2.06 % *vs.* 8.47 ± 1.63 %; $p$=0.830). Additionally, when compared to baseline data, the control group demonstrated non-significant differences in daily insulin doses after intervention (55.67 ± 17.41 IU *vs.* 56.53 ± 16.53 IU; $p$= 0.636). In contrast, the ALA group showed a significant decline in FBG and fructosamine levels from the first month to the end of the study (168.7 ± 21.12 mg/dl *vs.* 145.3 ± 12.45 mg/dl; $p$<0.001: 168.7± 21.12 mg/dl *vs.* 144.1 ± 12.69 mg/dl; $p$<0.001; 168.7 ± 21.12 mg/dl *vs.* 138.5 ± 16.56 mg/dl; $p$<0.001: 168.7 ± 21.12 mg/dl *vs.* 143.7 ± 13.85 mg/dl; $p$<0.001: 168.7 ± 21.12 mg/dl *vs.* 143.4 ± 12.32 mg/dl; $p$<0.001: 168.7 ± 21.12 mg/dl *vs.* 150.3 ± 25.70 mg/dl; $p$=0.001 for FBG and 568.7± 136.8 *vs.* 432.2 ± 103.1; $p$=0.004: 568.7 ± 136.8 *vs.* 416.5 ± 98.22; $p$<0.001: 568.7 ± 136.8 µmol/L *vs.* 363.0 ± 123.2 µmol/L; $p$<0.001: 568.7 ± 136.8 µmol/L *vs.* 413.8 ± 95.66 µmol/L; $p$<0.001: 568.7 ± 136.8 µmol/L *vs.* 413.6 ± 101.9 µmol/L; $p$<0.001: 568.7 ± 136.8 µmol/L *vs.* 437.3 ± 168.1 µmol/L; $p$<0.001 for fructosamine, respectively). Alpha-lipoic acid group demonstrated a non-significant decline in HbA1c after the third month (8.52 ± 1.35 % *vs.* 8.16 ± 1.88 %; $p$=0.900). However, this decline in glycated hemoglobin became significant at the end of the study (8.52 ± 1.35 % *vs.* 7.11 ± 1.20 %; $p$<0.001). Furthermore, when compared to baseline data, the ALA group experienced significant decline in in daily doses of insulin after intervention (61.83 ± 13.23 IU *vs.* 49.23 ± 11.08 IU; $p$<0.001), as shown in Table III.

The comparison of the two study groups after intervention revealed that the ALA group had significantly lower FBG than the control group at the first, second, and sixth months of intervention (159.0 ± 32.07 mg/dl *vs.* 145.3 ± 12.45 mg/dl; $p$=0.035, 158.4 ± 21.49 mg/dl *vs.* 144.1 ± 12.69 mg/dl; $p$=0.003 and 169.5 ± 24.16 mg/dl *vs.* 150.3 ± 25.70 mg/dl; $p$=0.004, respectively). Furthermore, when compared to the control group, the ALA group showed significantly lower glycated hemoglobin at the third and sixth months of intervention (9.35 ± 1.26 % *vs.* 8.16 ± 1.88 %; $p$=0.006 and 8.47 ± 1.63 % *vs.* 7.11 ± 1.20 %; $p$<0.001, respectively). Alpha-lipoic acid group showed also significantly reduced fructosamine level at the second, third and sixth months of intervention (516.7 ± 130.5 µmol/L *vs.* 416.5 ± 98.22 µmol/L; $p$=0.001, 425.3 ± 105.2 µmol/L *vs.* 363.0 ± 123.2 µmol/L; $p$=0.040 and 559.3 ± 154.9 µmol/L *vs.* 437.3 ± 168.1 µmol/L; $p$=0.005, respectively) compared to the control group. Furthermore, the ALA group had significantly lower daily insulin doses than the control group (56.53 ± 16.53 IU *vs.* 49.23 ± 11.08 IU; $p$=0.049). The comparison between the two groups is demonstrated in Table IV and Figure (2A and B).

### Clinical Outcome

At baseline, the two groups were statistically similar in respect to ankle-brachial index "ABI" (1.01 ± 0.10 *vs.* 1.06 ± 0.13; $p$=0.115), as shown in Table II. The stratification of patients postulated that 22 patients (73.3 %) in the control group *vs.* 16 patients (53.3%) in the ALA group had ABI 0.9-1 ($p$=0.108). Furthermore, 8 patients (26.7 %) in the control group *vs.* 14 patients (46.7 %) in the ALA group had ABI >1-1.4 ($p$=0.108), as demonstrated in Figure 3.

In comparison to baseline data, the control group showed non-significant variation in ABI 6 months after intervention (1.01 ± 0.10 *vs.* 1.0 ± 0.18; $p$=0.825). In contrast, alpha-lipoic acid group showed significant decline in ABI (1.06 ± 0.13 *vs.* 0.94 ± 0.04; $p$<0.001), as postulated in Table III. After intervention, the ALA group showed significantly lower mean value of ABI as compared to the control group (1.0 ± 0.18 *vs.* 0.94 ± 0.04; $p$=0.045), as shown in Table IV. The stratification of patients after intervention revealed that four patients (13.3%) in the control group *vs.* no-one (0%) in the ALA had ABI < 0.9 ($p$= 0.112), 24 patients (80%) in the control group *vs.* 30 patients (100%) in the ALA group had ABI 0.9-1 ($p$=0.024), and 2 patients (6.7%) in control group *vs.* no-one (0%) in the ALA group had ABI >1.4 ($p$=0.492), as demonstrated in Figure 3.

### Safety and Tolerability

The control group was statistically similar to ALA group in the number and percentage of patient who developed adverse effects which included headache [10 (33.3% ) *vs.* 11 (36.7 %); $p$=0.1468], itching/burning sensation [2 (6.7%) *vs.* 5 (16.7%); $p$=0.7357], skin rash [2 (6.7%) *vs.* 5 (16.7%); $p$=0.7357], and nausea/vomiting [4 (13.3%) *vs.* 5 (16.7%); $p$=0.5186].

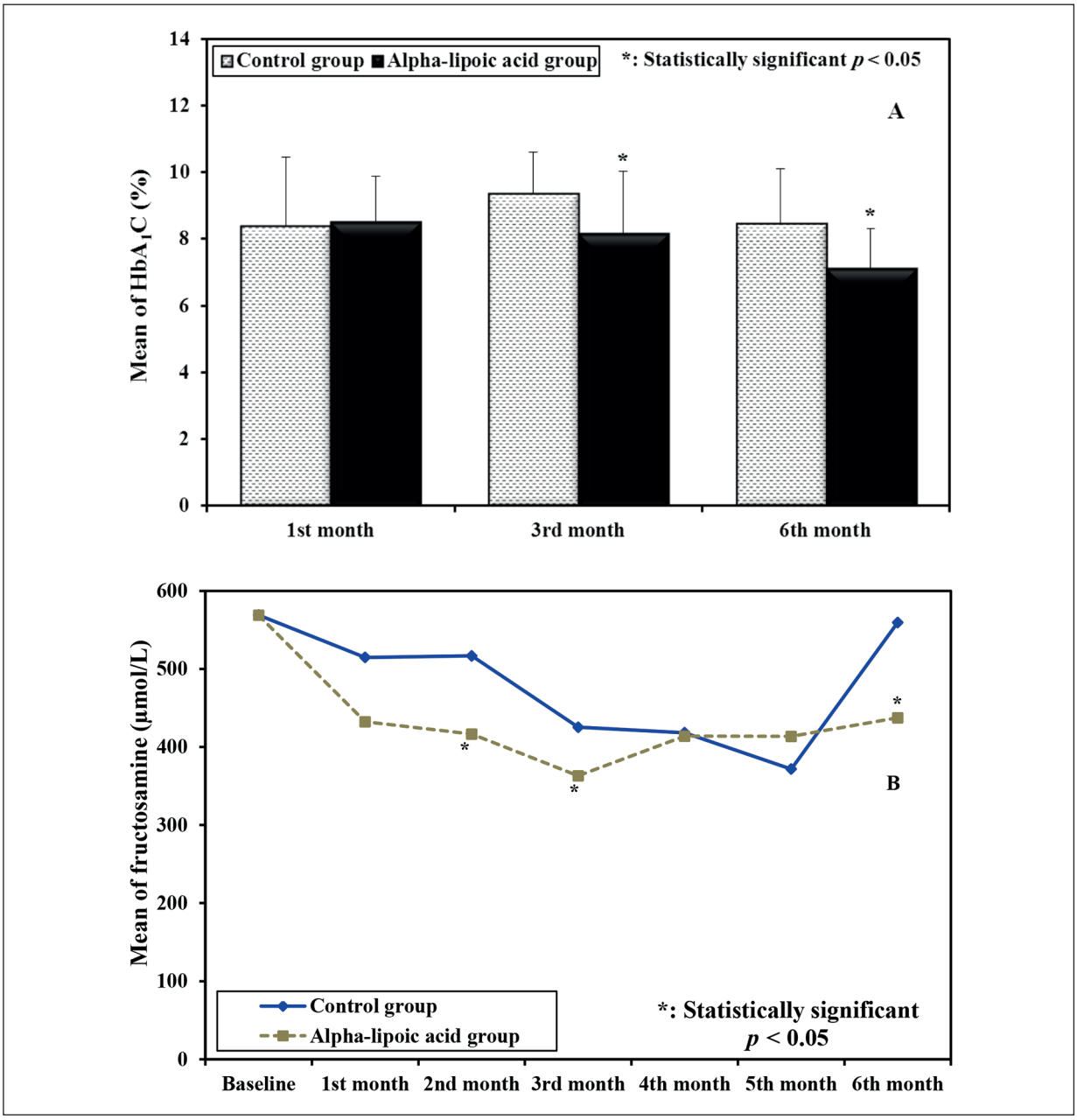


**Figure 2.** Glycated hemoglobin **(A)** and fructosamine level **(B)** for the two study groups during the course of the study.

### *Pharmaco-Economic Analysis*

At baseline, there was no statistically significant difference between the two study groups regarding the cost of weekly doses of alpha recombinant human erythropoietin (208.0 ± 74.0 LE *vs.* 200.2 ± 84.36 LE; $p$=0.464). Similarly, the total cost of weekly doses of iron, alpha recombinant human erythropoietin, insulin, and alpha-lipoic acid capsules (248.1 ± 75.58 LE *vs.* 264.2 ± 89.87 LE; $p$=0.456), as shown in Table II.

As compared to the baseline data, six months after the intervention, the control group showed non-significant differences in the cost of weekly doses of alpha recombinant human erythropoietin (208.0 ± 74.0 LE *vs.* 203.3 ± 84.15 LE; $p$=0.741). Similarly, and total cost of weekly doses of iron, alpha recombinant human erythropoietin, and insulin (248.1 ± 75.58 LE *vs.* 255.0 ± 96.64 LE; $p$=0.738). On the contrary, the ALA group demonstrated significant differences in the cost of

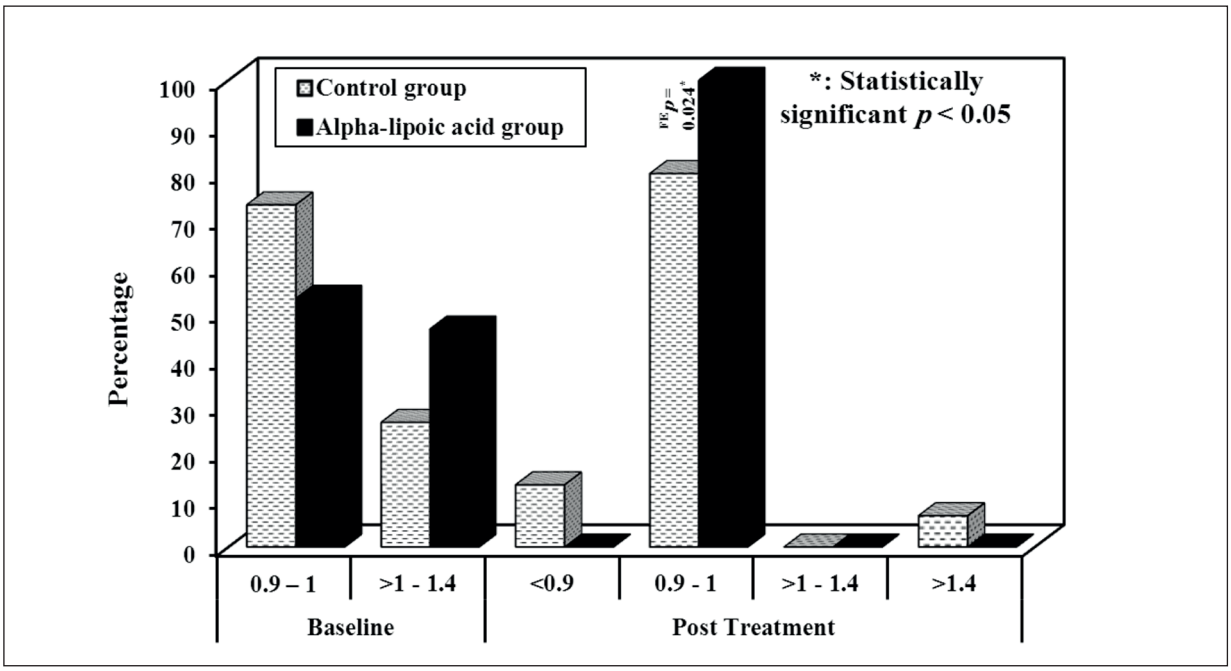


**Figure 3.** Ankle-brachial index (ABI) for the two study groups at baseline and at the end of intervention.

weekly doses of alpha recombinant human erythropoietin (200.2 ± 84.36 LE *vs.* 99.16±59.58 LE; $p<0.001$). Similarly, the total cost of iron, erythropoietin, insulin, and alpha-lipoic acid capsules (264.2 ± 89.87 LE *vs.* 149.5 ± 61.88 LE; $p<0.001$) showed substantial differences, as depicted in Table III. At the end of the study, the alpha-lipoic acid group showed a significant reduction in the cost of weekly doses of alpha recombinant human erythropoietin (203.3 ± 84.15 LE *vs.* 99.16 ± 59.58 LE; $p<0.001$) and in the total weekly cost (255.0 ± 96.64 LE *vs.* 149.5 ± 61.88 LE; $p<0.001$) compared to the control group, as postulated in Table IV.

## Discussion

This multi-center prospective randomized controlled study aimed at investigating the impact of alpha-lipoic acid (ALA) on inflammation, oxidative stress, anemia, and glycemic parameters and their association with cardiovascular risk in diabetic patients on hemodialysis. The dose of alpha-lipoic acid utilized in the current study was 600 mg/day, which corresponds to and is based on other previous studies[19,20]. The study duration was six months, which appears to be longer than other former studies and comparable to other studies[19-21]. However, hemodialysis did not significantly contribute to increased clearance of alpha-lipoic acid, and thus dose adjustment of alpha-lipoic acid seems unnecessary in patients with renal dysfunction[22]. During the current study, alpha-lipoic acid was used after dialysis sessions on days of dialysis.

The two groups had statistically similar anthropometric parameters (body weight and BMI) at baseline. At the end of the study, ALA failed to induce a significant change in body weight and BMI compared to both baseline data and the control group. This result seems in contradiction with a former study, which reported that oral administration of ALA 1200 mg/day for eight weeks induced significant but slight weight loss in overweight or obese subjects[23]. These contradictory results could be attributed to the variability of the implicated of ALA doses, the study populations, and the nature of the disease.

After the intervention, ALA induced a significant decline in inflammatory biomarkers (hs-CRP and TNF-α) and oxidative stress biomarker (8-OHdG) compared to baseline data ($p<0.001$) and compared to the control group ($p<0.001$). Alpha-lipoic acid has been shown to have an anti-inflammatory effect by suppressing kinase I Kappa B, a convergent enzyme that activates NF-kB, thereby inhibiting the production and release

of inflammatory cytokines[24]. Due to its dithiolane ring, ALA and its reduced form dihydro-lipoic acid (DHLA) form a potent redox couple and display an impressive array of antioxidant functions. Both forms have been reported to directly scavenge reactive oxygen species (ROS) and inhibit their formation by chelating transition metal ions, including $Fe^{2+}$ ion[25]. Alpha-lipoic acid recycles endogenous antioxidant enzymes and vitamins, including co-enzyme Q 10 (Q10) vitamins E and C[26]. Lipoic acid markedly increases intracellular glutathione (GSH), an abundant natural thiol antioxidant and co-substrate for detoxification enzymes in a variety of cell types[25]. Our results are consistent with the findings of a previous study, which demonstrated that ALA significantly decreased hs-CRP, TNF-α, and reactive oxygen species serum levels in diabetic patients with kidney disease and patients on hemodialysis[27,28]. However, some authors reported absence of significant effect of ALA on IL-8, TNF-α, and MDA serum levels, they can't deny the beneficial effects of ALA in patients on hemodialysis[19,20].

Six months after interventions, ALA significantly reduced uremic toxins; serum creatinine, urea, and blood urea nitrogen when compared to baseline data ($p<0.001$) and significantly reduced urea and blood urea nitrogen than the control group ($p=0.029$). Urea is a highly toxic substance, and its elevated concentration can result in the generation of reactive oxygen species[29]. The reactive oxygen species (ROS) likely contribute to apoptosis and progression of renal injury during chronic kidney disease[30]. Therefore, the beneficial effect of ALA on uremic toxin and kidney function may be attributed to its antioxidant activity, which consequently can provide a reno-protective effect[24,25,31]. Furthermore, the beneficial effect of ALA can be attributed to its anti-inflammatory effect because most CKD patients have a chronic inflammatory state and increased levels of inflammatory markers, such as C-reactive protein, interferon-gamma, and TNF-α. In addition, these inflammatory markers were reported to be associated with decreased kidney function[24]. This finding demonstrated that ALA could improve renal function in patients with diabetic kidney disease[27].

Renal anemia is becoming more common and severe in diabetic patients[32]. Renal anemia has a complicated etiology that includes decreased endogenous erythropoietin (EPO) production, absolute and/or functional iron deficiency, oxidative stress, inflammation, uremia toxins accumulation, and increased hepcidin levels[33]. Oxidative stress with subsequent destruction of the red blood cell membrane in hemodialysis patients can result in a decline in erythrocytes life span and could exaggerate anemia of renal failure[34]. Increased inflammatory cytokines have been correlated with erythropoietin resistance in patients with chronic kidney disease[35]. Elevated level of inflammatory cytokines (TNF-α and hs-CRP) can restrain erythroid progenitor cell production and can affect bone marrow hematopoiesis, leading to erythropoietin hypo-responsiveness and poor outcomes[36].

Moreover, uremia toxins accumulation is one of the causes of renal anemia[37,38]. The data obtained in the current study revealed that the implication of alpha-lipoic acid supplement induced a significant elevation in hemoglobin concentration, serum iron level, and transferrin saturation (TSAT) compared to the control group ($p<0.001$, $p=0.037$, and $p<0.001$, respectively). This improvement in anemia-related parameters following ALA intervention was associated with a significant decrease in monthly doses of iron ($p<0.001$), weekly doses of alpha recombinant human erythropoietin ($p<0.001$), and erythropoietin resistance index ($p<0.001$) compared to the control group. The aforementioned beneficial effects of ALA could be attributed to its antioxidant and anti-inflammatory activities and its beneficial effect on kidney function with subsequent reduction of uremia toxins[25,24,27]. Our results are compatible with former studies that demonstrated that ALA significantly elevated hemoglobin concentration and serum iron level[28]. Also, our data are in agreement with a former study, indicating that erythropoietin doses and the erythropoietin resistance index were significantly reduced in the ALA treated group compared to baseline data[20]. However, our finding seems in contradiction with the findings of other authors who postulated that ALA showed no effect on hemoglobin and hematocrit values[20]. These conflicting findings can be attributed to the differences in the study duration and the baseline hemoglobin levels for the enrolled patients.

Glycated hemoglobin (HbA1c) is accredited for long-term follow-up of glycemic control and diagnoses diabetes mellitus. HbA1c in hemodialysis patients is influenced by uremia, mechanical hemolysis, and hematopoiesis, which includes both iron status and erythropoietin-stimulating agent dose[9]. In addition, the assessment of HbA1c is biased or even unreliable, especially in patients

with rapid changes of glucose homeostasis, more extensive glycemic excursion, red blood cell disorders, and chronic kidney diseases[39]. In this context, fructosamine and other non-traditional markers of hyperglycemia, including glycated albumin, are valued since they are not influenced by erythrocyte turnover that may result from mechanical hemolysis, stimulated erythropoiesis, and bleeding[10]. Concerning glycemic panel and as compared to the control group, ALA supplement resulted in a significant decline in fasting blood glucose (FBG) level at first, second and sixth months ($p$=0.035, $p$=0.003, $p$=0.004 respectively), HbA1c concentration at the third and sixth months ($p$=0.006 and $p$<0.001, respectively) and fructosamine level at second, third and sixth months ($p$=0.001, $p$=0.04 and $p$= 0.005, respectively). This beneficial effect of ALA on glycemic parameters was associated with a significant decrease in daily doses of insulin ($p$<0.001). Alpha-lipoic acid can decrease FBS and HbA1c levels, probably by increasing glucose transporter (GLUT-4) translocation to the muscle and fat cell membranes with a subsequent increase of glucose uptake[40]. Alpha-lipoic acid was reported to suppress hepatic gluconeogenesis[41]. It has been demonstrated that ALA can exert an insulin-mimetic effect since it partially improves insulin metabolic pathways through enhancing the activity of some proteins of the insulin signaling pathway such as insulin receptor (IR), insulin receptor substrate 1 (IRS1), phosphatidylinositide 3-kinase (PI3K), and protein kinase B "AKT"[40]. In addition, the beneficial effect of ALA on glycemic parameters may be related to its anti-inflammatory effect and its suppressive effect on both TNF-α and hs-CRP because inflammation is usually associated with diabetes. The favorable impact of ALA on glycemic parameters may be attributed to its antioxidant activity since oxidative stress was reported to be linked to insulin resistance[7]. Our results are in the same line with formerly reported findings demonstrated that oral treatment with ALA caused amelioration of HbA1c in diabetic patients[42].

Furthermore, a meta-analysis revealed the significant beneficial effect of ALA on fasting blood glucose and HbA1c[43]. Additionally, it was postulated that ALA effectively reduced fructosamine levels in patients with type 2 diabetes[44]. Other authors reported the ability of ALA to reduce fructosamine levels, which was directly correlated with a reduction in the formation of advanced glycation end-products[45].

The ankle-brachial index (ABI) was used to assess the clinical outcome. ABI has been reported to be independently associated with all causes of mortality including cardiovascular disease-related mortality in hemodialysis patients, in addition to being a quick, non-invasive test for peripheral artery disease, and has the potential to screen coronary artery disease[16,17,46]. An ABI <0.9 was widely acknowledged to indicate an abnormally low level, and a high ABI value was defined as ABI >1.4, suggesting arterial stiffness[47,48]. There was non-significant difference between the two study groups concerning ABI at baseline. Six months after the intervention, the mean value of ABI was significantly lower in the ALA group compared to the control group ($p$=0.045), where all patients (100%) in ALA reported acceptable ABI (0.9-1) *vs.* 80% in the control group ($p$=0.024), which consistent to a previous report stating that ABI (0.9-1) is acceptable[49]. In addition, four patients (13.3%) in the control group showed ABI <0.9 *vs.* no one (0%) in the ALA group; however, this difference is statistically non-significant ($p$=0.112), it seems clinically important. The overall results indicate that patients in the ALA group were less susceptible to cardiovascular events than those in the control group. Previous research has shown that a low ABI (<0.9) has a high specificity for predicting cardiovascular outcomes and an increased risk of cardiovascular mortality[47,50]. Furthermore, hs-CRP and TNF-α have been found to be correlated with increased risk for cardiovascular disease[51,52]. Oxidative stress may contribute to the pathogenesis of CVD in patients with CRF[53]. Anemia is considered a contributing factor to cardiovascular diseases. Patients with higher erythropoietin resistance index (ERI) values have a higher cardiovascular mortality rate due to increased blood viscosity and endothelial stress[54,55]. Additionally, there is an association between the administration of high doses of erythropoietin stimulating agents and the increased risk of cardiovascular complications[5]. Alpha-lipoic supplementation reduced the administered doses of iron, which is well known to induce severe oxidative stress and tissue damage secondary to its ability to receive and transfer electrons[56]. Furthermore, high HbA1c values are correlated with macro-vascular and microvascular complications, as well as higher cardiovascular mortality rates in diabetic patients on hemodialysis[8]. Additionally, elevated fructosamine level is considered a risk factor for

cardiovascular events in patients on dialysis[11]. In this context and according to the data obtained with the current study, ALA may reduce the risk of cardiovascular disease in diabetic patients on hemodialysis through its favorable and significant effects on inflammatory markers (hs-CRP and TNF-α), oxidative stress biomarker (8-OHdG), anemia, iron doses, erythropoietin doses, and erythropoietin resistance. In addition, the beneficial effect of ALA on glycemic parameters, including FBG, HbA1c, and fructosamine, may induce a cardio-protective effect. Some former studies postulated the cardio-protective effect of ALA, which can support the findings and suggestions obtained with the current study[28,57].

Alpha-lipoic acid was well tolerated and did not provoke severe adverse effects. The reported adverse effects were mild and transient, included headache, itching, nausea/vomiting, and numbness. These reported adverse effects were statistically similar to those of the control group ($p$>0.05). Our results are compatible with a systematic review and meta-analysis of 71 randomized placebo-controlled clinical studies, which demonstrated that ALA supplementation was safe, even in subsets of studies categorized according to smoking habit, cardiovascular disease, the presence of diabetes, pregnancy status, neurological disorders, rheumatic affections and severe renal impairment[58]. Furthermore, other authors postulated the safety and tolerability of ALA in patients with type 2 diabetes[44].

According to the pharmaco-economic analysis, nonetheless, it appears that we added another supplement to the treatment protocol. The comparison between the ALA group and the control group revealed that the ALA supplement resulted in a significant decline in the cost of weekly doses of erythropoietin ($p$ <0.001). Moreover, it induces a significant decline in the total weekly cost of iron, erythropoietin stimulating agent, insulin, and ALA capsules ($p$<0.001). This favorable pharmaco-economic impact of ALA could be attributed to its beneficial effects on anemia, erythropoietin resistance, and its ability to maintain glycemic control.

The current study's strengths include its multi-center design and the assessment of the pharmaco-economic impact of ALA on the cost of weekly doses of erythropoietin and the total cost of the medications involved. However, the study has some limitations, such as the use of a fixed-dose of ALA and a relatively small sample size.

### Study Limitations

The current study lacks the assessment of direct measures for cardiovascular outcomes such as echocardiography and evaluation of brain natriuretic peptides. Other limitations of the present study include the use of a fixed-dose of ALA and the relatively small sample size.

## Conclusions

The current study's findings revealed that alpha-lipoic acid (600 mg/day) was well tolerated and provided anti-inflammatory and antioxidant activity with subsequent improvement of anemia and maintenance of glycemic control. Additionally, the alpha-lipoic acid supplement improved erythropoietin resistance, resulting in subsequent reduction in the weekly doses of erythropoietin stimulating agent. Furthermore, ALA may provide cardio-protection through its overall beneficial effects and its favourable impact on the ankle-brachial index. The implication of alpha-lipoic acid supplement in diabetic patients on hemodialysis provided a pharmaco-economic benefit through reducing the cost of weekly doses of erythropoietin stimulating agent and the total cost. Despite these results, further large-scale studies involving different doses of ALA are urgently required for complete evaluation of its effects in diabetic patients on hemodialysis.

### Conflict of Interest

The Authors declare that they have no conflict of interests.

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### Authors' Contribution

Tarek M. Mostafa, Yasser A. Nienaa and Dina Z. Abdel Hamid reviewed the literature and constructed the study design. Eligibility and enrolment of the study participants were done by Yasser A. Nienaa. Laboratory analysis was done by Dina Z. Abdel Hamid and Tarek M. Mostafa. Dina Z. Abdel Hamid carried out statistical analyses. All authors wrote, revised, and approved the final version of the manuscript.

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