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Review

Alpha Lipoic Acid Supplementation and Iron Homeostasis: A Comprehensive Systematic Review and Meta-Analysis of Randomized Controlled Clinical Trials

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Abstract

Background: A growing body of evidence indicates the regulating effects of alpha-lipoic acid on iron metabolism. However, findings from clinical trials are equivocal. This systematic review and meta-analysis aimed to evaluate the quantitative effect of alpha lipoic acid (ALA) supplementation on iron metabolism parameters including serum iron, total iron binding capacity, hemoglobin, and ferritin. **Methodology**: Online databases, including PubMed, Scopus, and Web of Science were searched, up to 29 May 2022, to obtain all relevant studies. **Results**: A total of 1901 publications were identified in the systematic search; of which, 10 studies with a total of 529 participants were included in this meta-analysis. Pooled analysis of the studies showed no statistically significant effects of ALA on ferritin (weighted mean difference (WMD) = –11.01 ng/mL; 95% CI: –40.07, 18.05 ng/mL; $I^2 = 0.0\%$, $p = 0.670$), serum iron (WMD = –0.47 µ/dL; 95% CI: –24.48, 23.54 µ/dL; $I^2 = 94.7\%$, $p < 0.001$), hemoglobin (WMD = 0.49 g/dL; 95% CI: –0.54, 1.52 g/dL; $I^2 = 95.7\%$, $p < 0.001$), and total iron binding capacity (TIBC) (WMD = 3.95 µ/dL; 95% CI: –21.3, 29.2 µ/dL; $I^2 = 53.1\%$, $p = 0.094$). In subgroup analysis, ALA significantly increased hemoglobin in patients with hematological disorders (WMD = 1.23 g/dL; 95% CI: 1.00, 1.45 g/dL; $I^2 = 96.6\%$, $p < 0.001$) and in studies with durations longer than 8 weeks (WMD = 1.03 g/dL; 95% CI: 0.82, 1.25 g/dL; $I^2 = 96.5\%$, $p = 0.02$). **Conclusion**: ALA supplementation had no statistically significant effect on iron-related parameters. Subgroup analysis revealed a significant increasing effect of ALA on hemoglobin in patients with hematological disorders and in studies with durations >8 weeks.

Keywords: thioctic acid; ferritin; hemoglobin; iron overload; systematic review

1. Introduction

Alpha lipoic acid (ALA) is an endogenous short-chain fatty acid that acts as a cofactor for mitochondrial dehydrogenase complexes [1]. In addition to endogenous synthesis, this organosulfur compound is supplied exogenously in the human diet [2]. Common dietary sources of ALA include muscle meats, heart, kidney, and liver. However, it is also found in a lesser amount in fruits and vegetables [3,4]. The amount provided by dietary intake typically ranged from 0.1 µg/g to 4 µg/g [5,6]. Alpha-lipoic acid exhibits antioxidant, anti-inflammatory, and iron chelator properties and has attracted considerable clinical interest as a therapeutic agent for several diseases, such as cardiovascular diseases, hypertension, renal diseases, and diabetes [7–9]. The therapeutic effects of ALA in humans seem to be at doses ranging from 200 to 1800 mg/d and, at doses up to 1800–2400 mg/day it can be tolerated safely without significant adverse effects [10]. ALA is reduced to dihydrolipoic acid (DHLA) after being taken up by cells and tissues. Both ALA and DHLA do iron-chelating activities and have the ability to scavenge reactive oxygen species (ROS) [11]. Nevertheless, there is some evidence of the prooxidant activity of redox couple ALA/DHLA especially in the presence of iron [12,13]. Iron is a redox-active element, which can enhance oxidative stress by the generation of oxygen free radicals via Fenton reaction [14,15]. Therefore, to ameliorate the toxic effects of iron, it is usually bonded with proteins such as transferrin, as it occurs in serum, or ferritin in the intracellular section [16]. However, extensive oxidative stress can enhance proteins needed for iron uptake, which in turn causes excessive catalytic iron levels and consequent iron-induced tissue damage [17,18]. Given the potential of ALA in the reduction of iron in cells and tissues, it may be considered as a treatment for ameliorating oxidative damage [19]. So far, several studies have evaluated the effects of ALA on iron-related factors including, ferritin, hemoglobin and total iron binding capacity (TIBC) [2,9,20]. Findings from primary studies indicated the protective role of ALA on iron overload and related oxidative stress [11,20]. Nevertheless, results from clinical trials are controversial. El-Nakib *et al.* [21] in a study that was conducted on end-stage renal disease patients undergoing hemodialysis reported that supplementation with 600 mg/d ALA for 3 months had no significant effects on hemoglobin and iron store indices, although the required doses of erythropoietin (EPO) was reduced. Conversely, in a study by Mendes *et al.* [22], a daily intake of 600 mg ALA for 12 weeks significantly re-

duced serum levels of iron and TSI (Transferrin Saturation Index) in hypertensive patients. These controversial findings might be attributed to the heterogeneities between studies regarding participants' health status, dose of ALA administered, and intervention duration. Hence, performing a systematic review and meta-analysis to assess the quantitative effect of ALA on Iron metabolism parameters, taking the heterogeneities among studies into account, would be worthwhile. However, until now, no such study has been conducted regarding this issue. Therefore, this meta-analysis was designed to evaluate and quantify the effect of ALA supplementation on iron homeostasis-related markers including serum iron, total iron binding capacity (TIBC), hemoglobin (Hgb), and ferritin.

2. Methods and Material

2.1 Search Strategy

This systematic review was performed according to the Preferred Reporting Items in Systematic Reviews and Meta-Analyses (PRISMA) guidelines [23]. A comprehensive and systematic literature search was performed in online literature databases including PubMed, Scopus, and Web of Science from inception up to 29 May 2022 to determine relevant publications. Relevant MeSH (Medical Subject Headings) terms related to alpha lipoic acid were searched in combination with parameters related to iron metabolism (**Supplementary Table 1**). In addition, the first 4 pages of Google Scholar and the references lists of relevant studies and recent reviews were assessed to find other, potentially, eligible studies. The publication search was not limited by language or date set on databases.

2.2 Eligibility Criteria

One researcher (ESZ) searched the mentioned online databases to retrieve potentially related studies. Titles, abstracts, and full texts of the retrieved studies were screened independently by the two authors according to the following inclusion criteria: (1) all randomized controlled trials (RCTs) that considered ALA as an intervention, (2) studies in which the comparator was no treatment, a placebo, or standard treatment, (3) those that considered the serum level of iron, TIBC, ferritin, and Hgb as outcomes, and (4) publications in which mean $\pm$ standard deviation (SD), mean $\pm$ standard error (SE), or mean (95% CI) were used to report the related effect sizes. In this review, publications were excluded if the effect of ALA was not independently examined, there was no appropriate control group or no randomization process, the information for the dosage and duration of the intervention was not provided, RCTs involving pregnant or lactating women and studies in languages other than English. Non-clinical studies, reviews, meta-analyses, and publications with no available full-text were also excluded.

2.3 Data Extraction

After screening and reading the selected articles, all data was independently extracted by the two researchers using a predefined form. Extracted data for each included study were as follows: first author name, year of study publication, country or region, study design, sample size, subjects' characteristics, dose and type of intervention, follow-up duration and outcome. Any disagreement regarding data extraction was resolved by discussion.

2.4 Quality Assessment

Quality and risk of bias for included studies were evaluated by the Cochrane Risk of bias assessment tool [24]. The assessment was performed based on the following criteria: selection bias (random sequence generation and allocation concealment), performance bias (blinding of participants and researcher), detection bias (blinding of outcome assessment), attrition bias (incomplete outcome data), reporting bias (selective outcome reporting), and any other bias (adjustment for baseline variables and dietary intake). The quality of studies was identified as poor (low risk for less than four domains), fair (low risk for four domains), and good (low risk for more than four domains), respectively. Any disagreements regarding the risk of bias were discussed and resolved by consultation.

2.5 Data Synthesis and Analysis

Mean differences (MD) for ferritin, serum iron, Hgb, and TIBC with their corresponding standard deviations (SDs) between intervention and control groups, in each study were used to calculate the effect size for ferritin, serum iron, Hgb, and TIBC. The weighted mean difference (WMD) and its corresponding SD for each variable were determined and pooled using the DerSimonian and Laird method [25], considering between-study heterogeneity. Between-studies heterogeneity was assessed using Cochrane's Q statistic and I-squared statistic [26]. Subgroup analyses, according to the dose of ALA ($<$600 mg/d and $\geq$600 mg/d), participant's health status (Hematological and Non-Hematological disorders), and study duration ($\leq$8 weeks and $>$8 weeks) were conducted to determine the heterogeneity between studies. Sensitivity analysis to evaluate the impact of a single study on the results was carried out by removing studies from the analysis, one by one. We also performed sensitivity analysis to detect the effect of methodological differences in relation to dosing and administration of ALA. Publication bias was examined through visual inspection of funnel plots as well as Egger's regression test. Stata software (version 14.0; Stata Corporation, LP, College Station, TX, USA) was used to conduct the meta-analysis. Statistical significance was accepted at $p < 0.05$.

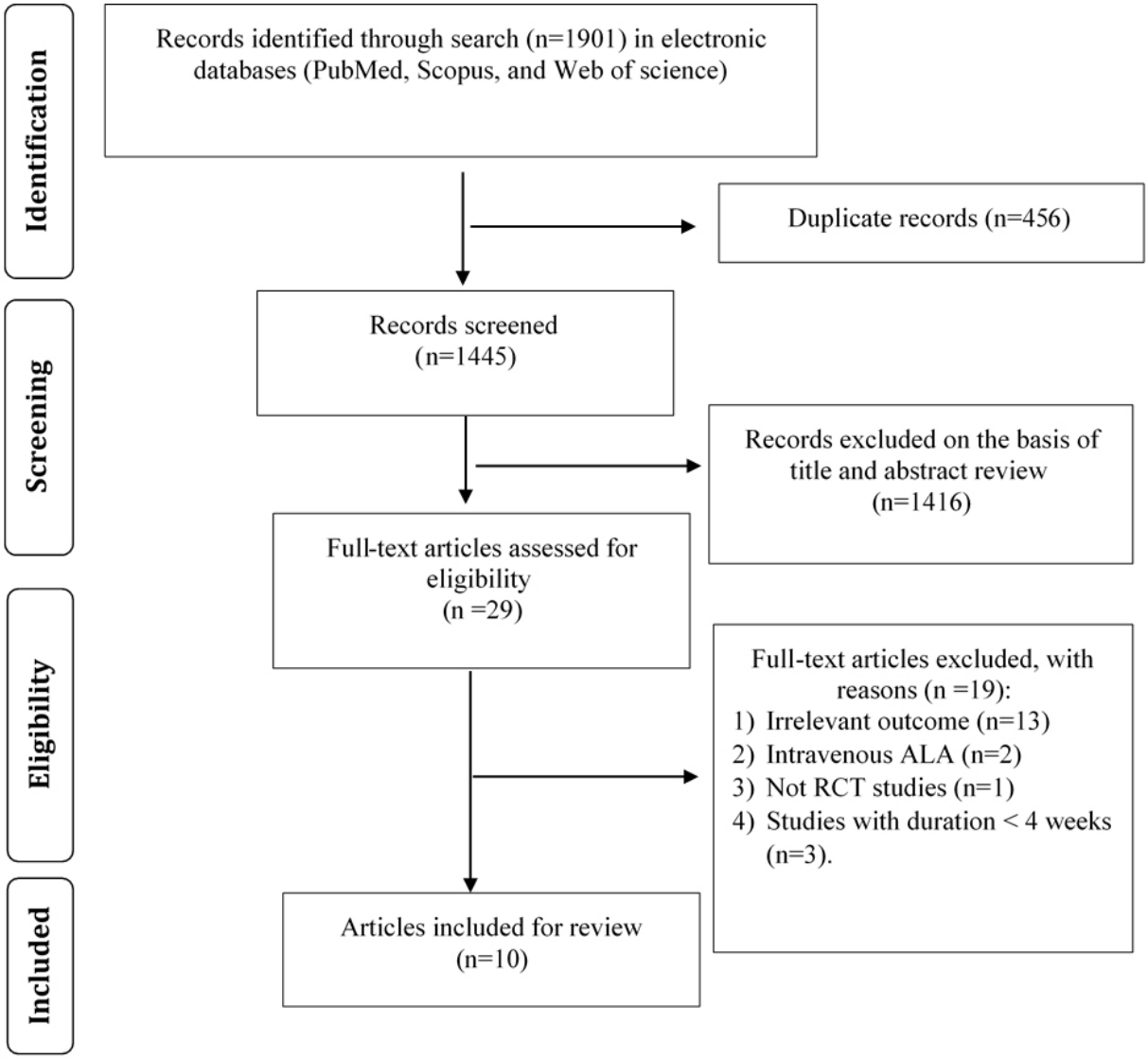

Fig. 1. Flow diagram of the literature search and study selection process.

3. Results

3.1 Study Characteristics

Fig. 1 shows the detailed processes of study selection. Overall, 1901 publications were initially retrieved from the online databases, of which, 456 duplicate and 1416 irrelevant articles were excluded based on title and abstract screening. Of the remaining 29 articles, an additional 19 were removed for the reasons mentioned in Fig. 1. Finally, 10 RCTs were included in this systematic review and meta-analysis. Table 1 (Ref. [7,13,21,22,27–32]) summarizes the main characteristics of the included studies. Of the 10 included studies, eight had a parallel design and two had a cross-over design. The duration of intervention varied from 8 weeks to 24 weeks, and ALA doses ranged from 200 mg/d to 1200 mg/d. Five studies were conducted on patients undergoing hemodialysis [7,21,27–29], one on hypertensive subjects [22], one on obese patients with NAFLD (non-alcoholic fatty liver) [30] and two on β-TM patients [31,32]. The study by Abdel Hamid *et al.* [7] had a different protocol for ALA supplementation (600 mg/d, three times per week), hence the daily dose of ALA was calculated and used in subgroup analysis. In addition, the study by Martins *et al.* [13], which enrolled three different populations was considered as three separate studies. Geographically, these 10 studies originated from Korea (n = 1), Brazil (n = 2), Egypt (n = 3), and Iran (n = 4).

3.2 Assessment Risk of Bias

Of the ten included studies, four studies had good quality based on Cochrane Collaboration's tools, five were classified as poor and one study received a fair score. Five studies for the method of random sequence generation and six for processes to conceal the allocation of participants had unclear risks of bias. Four studies did not indicate the

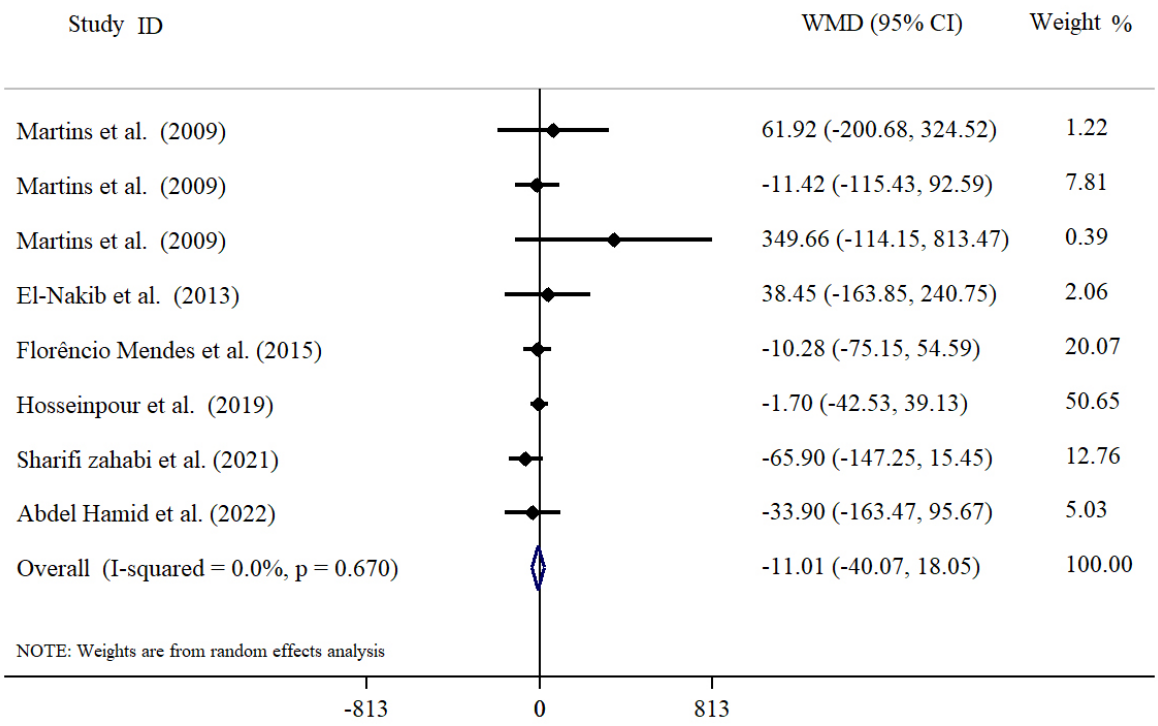

Fig. 2. Effect of alpha lipoic acid on ferritin. WMD, weighted mean difference.

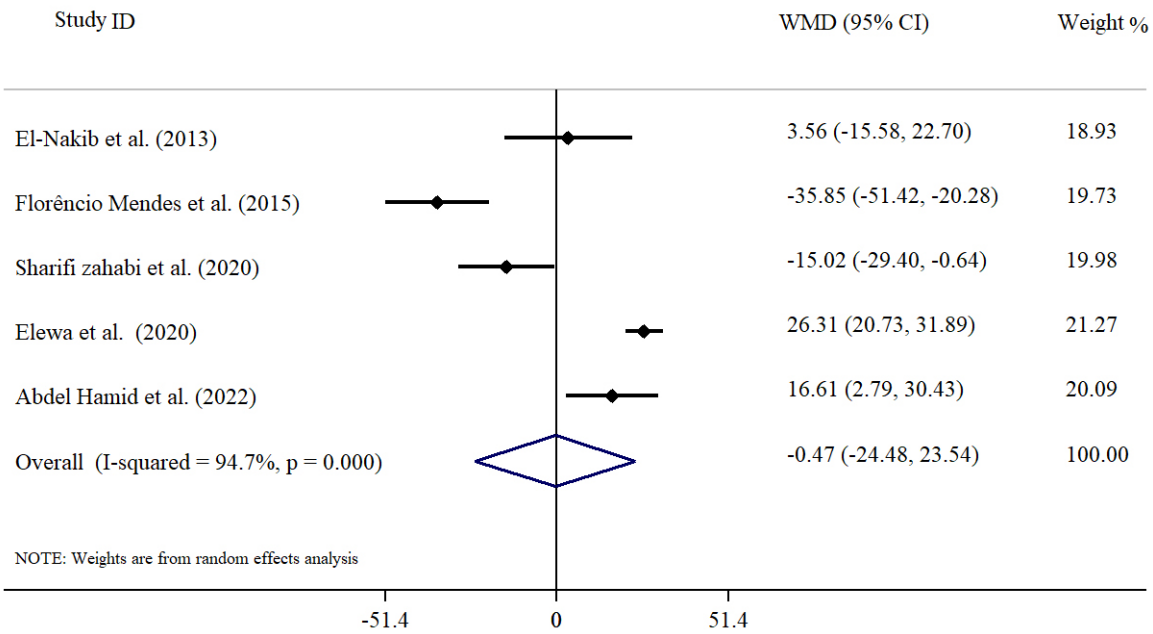

Fig. 3. Effect of alpha lipoic acid on serum iron. WMD, weighted mean difference.

blinding of participants and outcome assessment. Three studies had selective reporting bias and six studies had other biases (**Supplementary Fig. 1**).

3.3 ALA and Ferritin

Six studies with eight effect sizes assessed the effect of ALA on ferritin levels. The overall analysis showed no significant changes in ferritin levels in subjects treated with ALA compared to control (WMD = –11.01 ng/mL; 95% CI: –40.07, 18.05 ng/mL). The heterogeneity between studies was low ($I^2 = 0.0\%$, $p = 0.670$) (Fig. 2). This result was also observed across all subgroups ($p > 0.05$) (**Supplementary Table 2**). Although visual inspection of the funnel plot showed evidence of asymmetry, there was no publication bias among studies based on Egger's test ($p = 0.354$).

Table 1. Main characteristics of studies examining the effect of ALA on Hematological indices.

Author. date	Country	Study design	Subjects, n, T/C	Subject characteristic	Dose and Type intervention	Duration (week)	Results	Total score
Chang *et al*. 2007 [29]	Korea	Parallel RCT	25/25	End-Stage Renal Disease Patients on Hemodialysis	600 mg/d ALA *vs.* placebo	12	No significant effects on Hgb.	2
Mendes *et al*. 2015 [22]	Brazil	DB Parallel RCT	32/28	Hypertensive subjects	600 mg/d ALA *vs.* placebo	12	Significant reduction in serum iron. No significant effects on TIBC, Hgb and ferritin.	4
El-Nakib *et al*. 2013 [21]	Egypt	Parallel RCT	22/22	End stage renal disease patients undergoing hemodialysis	EPO + ALA 600 mg/d *vs.* EPO	12	No significant effects on Hgb, TIBC, serum iron and ferritin.	2
Martins *et al*. 2009 [13]	Brazil	Parallel RCT	30/30	-Normal subjects -Sickle cell trait subjects -Sickle cell patients	200 mg/d ALA *vs.* placebo	12	No significant effects on hematological indices.	2
Hosseinpour-Arjmand *et al*. 2019 [30]	Iran	DB Parallel RCT	23/22	Obese patients with NAFLD	vitamin E + 1200 mg/d ALA *vs.* Vitamin E + placebo	12	No significant effects on ferritin.	7
Mahdavi *et al*. 2019 [28]	Iran	DB Parallel RCT	24/28	Hemodialysis patients	600 mg/d ALA *vs.* placebo	8	No significant effects on Hgb.	7
Sharifi-Zahabi *et al*. 2020 [32]	Iran	Cross-over DB RCT	22/22	β-TM patients	600 mg/d ALA *vs.* placebo	8	No significant effects on TIBC, Hgb and serum iron.	6
Elewa *et al*. 2020 [27]	Egypt	DB Parallel RCT	35/35	Hemodialysis patients	600 mg/d ALA *vs.* placebo	12	Significant elevations in Hgb concentration and serum iron.	3
Sharifi-Zahabi *et al*. 2021 [31]	Iran	Cross-over DB RCT	22/22	β-TM patients	600 mg/d ALA vplacebo	8	Significant reduction in ferritin.	6
Abdel Hamid *et al*. 2022 [7]	Egypt	Parallel RCT	30/30	Diabetic patients on hemodialysis	257 mg/d ALA + EPO + insulin therapy *vs.* EPO + insulin therapy	24	Significant elevations in Hgb concentration and serum iron.	3

Abbreviation: ALA, alpha lipoic acid; n, number; T, treatment; C, control; DB, double-blinded; RCT, randomized controlled trial; NAFLD, non-alcoholic fatty liver; β-TM, β-thalassemia major; EPO, erythropoietin; Hgb, hemoglobin; TIBC, total binding capacity.

3.4 ALA and Serum Iron

Five studies addressed the effect of ALA on serum iron. The overall analysis indicated no significant changes in serum iron levels in subjects treated with ALA (WMD = –0.47 µ/dL; 95% CI: –24.48, 23.54 µ/dL). The heterogeneity was high (I^2 = 94.7%, $p < 0.001$) (Fig. 3). Subgroup analysis for serum iron was not possible due to the limited number of studies. In contrast to the visual inspection of the funnel plot that showed evidence of asymmetry, there was no publication bias among studies according to Egger's test ($p = 0.107$).

3.5 ALA and Hgb

Eight studies with ten effect sizes assessed the effect of ALA on Hgb level. The overall analysis showed no significant changes in Hgb levels in subjects treated with ALA compared to control (WMD = 0.49 g/dL; 95% CI: –0.54, 1.52 g/dL). However, the heterogeneity between studies was high ($I^2 = 95.7\%, p < 0.001$) (Fig. 4). Subgroups analysis revealed that ALA could significantly increase Hgb in patients with hematological disorders (WMD = 1.23 g/dL; 95% CI: 1.00, 1.45 g/dL; $I^2 = 96.6\%, p < 0.001$) and in studies with durations >8 weeks (WMD = 1.03 g/dL; 95% CI: 0.82, 1.25 g/dL; I^2 = 96.5%, $p = 0.02$). (**Supplementary Table 2**). Although visual inspection of the funnel plot showed evidence of asymmetry, there was no publication bias among studies based on Egger's test ($p = 0.320$).

3.6 ALA and TIBC

Four studies evaluated the effect of ALA on TIBC. Combining the effect sizes of these studies revealed no significant differences in TIBC level in subjects treated with ALA compared to control (WMD = 3.95 µ/dL; 95% CI: –21.3, 29.2 µ/dL), and the heterogeneity between studies was high ($I^2 = 53.1\%, p = 0.094$) (Fig. 5). Subgroup analysis for TIBC was not possible due to the limited number of studies. Visual inspection of the funnel plot showed evidence of asymmetry, however, Egger's test showed no publication bias among studies ($p = 0.294$).

3.7 Sensitivity Analysis

We sequentially removed each trial from the analysis to perform sensitivity analysis. Since one of the included studies [7] had a different protocol for ALA supplementation (600 mg/d, three times weekly), we also conducted the sensitivity analysis in the absence of this study and found that no study had a noticeable impact on the overall effect size.

4. Discussion

To the best of our knowledge, this systematic review and meta-analysis is the first one that assessed the quantitative effect of ALA on iron metabolism parameters. The pooled results of this study revealed that ALA supplementation, in comparison with the control, could reduce ferritin by 11.01 ng/mL and serum iron by 0.47 µg/dL. Additionally, ALA supplementation increases Hgb and TIBC by 0.49 g/dL and 1.23 g/dL respectively. However, none of these effects were statistically significant. Subgroup analysis, based on the participant's health status and intervention duration showed that ALA could enhance Hgb by 1.23g/dL and 1.03 g/dL in patients with hematological disorders and in studies with durations longer than 8 weeks respectively. Our sensitivity analysis also revealed that excluding a single study had no significant effect on the overall result. As a metal chelator agent, ALA may have regulating effects on factors related to iron metabolism [2,11,20]. Goralska *et al*. [11] in a study on human lens epithelial cells indicated that supplementation with lipoic acid decreases the concentration of free iron, reduces the iron uptake from transferrin, and increases iron deposition into ferritin, leading to an increase in the concentration of this protein. Moreover, Mendes *et al*. [22] showed that supplementation with 600 mg/day ALA for 12 weeks in hypertensive patients had no statistically significant effects on transferrin saturation index, TIBC, and serum levels of iron. However, *Cohen's d* coefficient revealed that ALA had clinically significant effects (>0.8) on above-mentioned variables, when compared to the control group. In this regard, our results may also indicate that the effect of ALA on iron metabolism parameters was not clinically significant as the obtained WMDs were lower the *Cohen's d* reported by Mendes *et al*. [22]. Differences in the health status of studies' participants and also the small number of included studies may contribute to the discrepancies observed between this meta-analysis and the previous study. Ferritin is an acute-phase protein that can increase in response to the inflammatory process independent of iron status [33,34]. Inflammation usually decreases the predictive values of ferritin for iron stores status [35]. As the majority of the included studies in this meta-analysis assessed the effect of ALA on iron metabolism parameters in participants with a pathological condition or chronic inflammatory state, the reduction effects of ALA on ferritin might be related to its anti-inflammatory and antioxidant activity [36]. Hence, assessing of serum levels of C-reactive protein (CRP) may be required to better discern the effect of ALA on iron stores [37]. However, this issue was not considered in most of the evaluated studies. Additionally, the non-significant reduced level of ferritin observed in this meta-analysis may be attributed to the chelating effect of ALA which can lead to a diminish in serum iron, cellular concentration of iron, and its binding to ferritin, as a storage protein.

In patients undergoing hemodialysis and receiving EPO, administration of ALA at the dose of 600 mg/day resulted in no significant effect on Hgb and iron store indices. Generally, patients in this study were considered non-anemic, with few Hgb values below 10.5 g/dL [21]. Therefore, the effect of ALA on iron-related parameters might be dependent on the baseline values of these param-

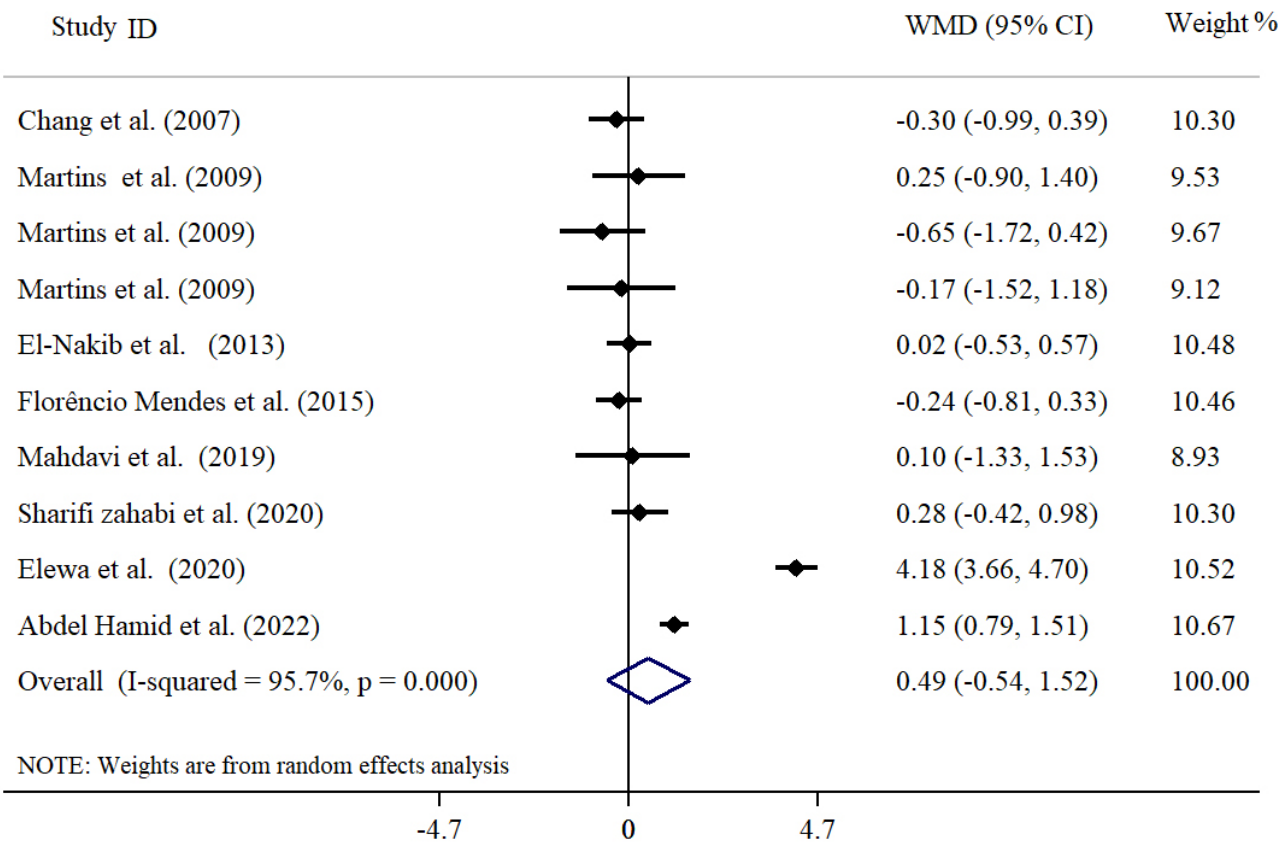

Fig. 4. Effect of alpha lipoic acid on Hgb. WMD, weighted mean difference; Hgb, hemoglobin.

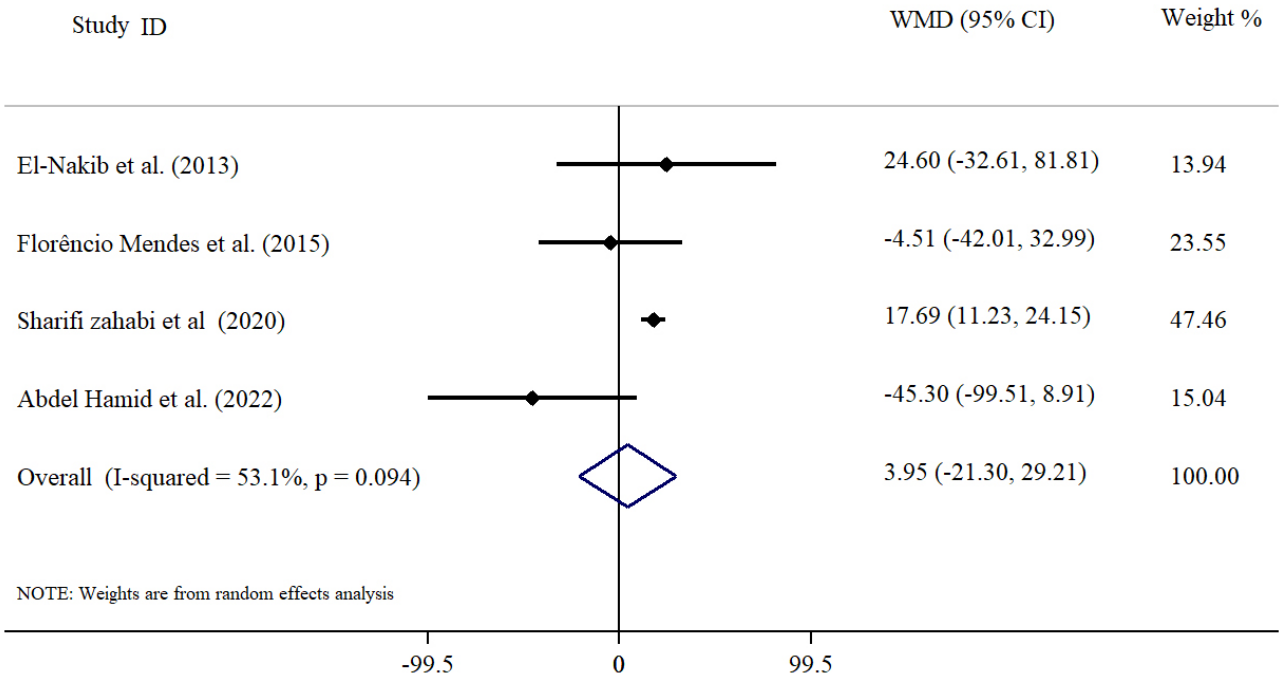

Fig. 5. Effect of alpha lipoic acid on TIBC. WMD, weighted mean difference; TIBC, total iron binding capacity.

eters. In this regard and consistent with our subgroup analysis, Abdel Hamid *et al.* [7] in a study on anemic diabetic patients on hemodialysis revealed that ALA had a significant increasing effect on Hgb. The same results were also observed in a study by Elewa *et al.* [27] on anemic hemodialysis patients. Inflammatory cytokines may have a

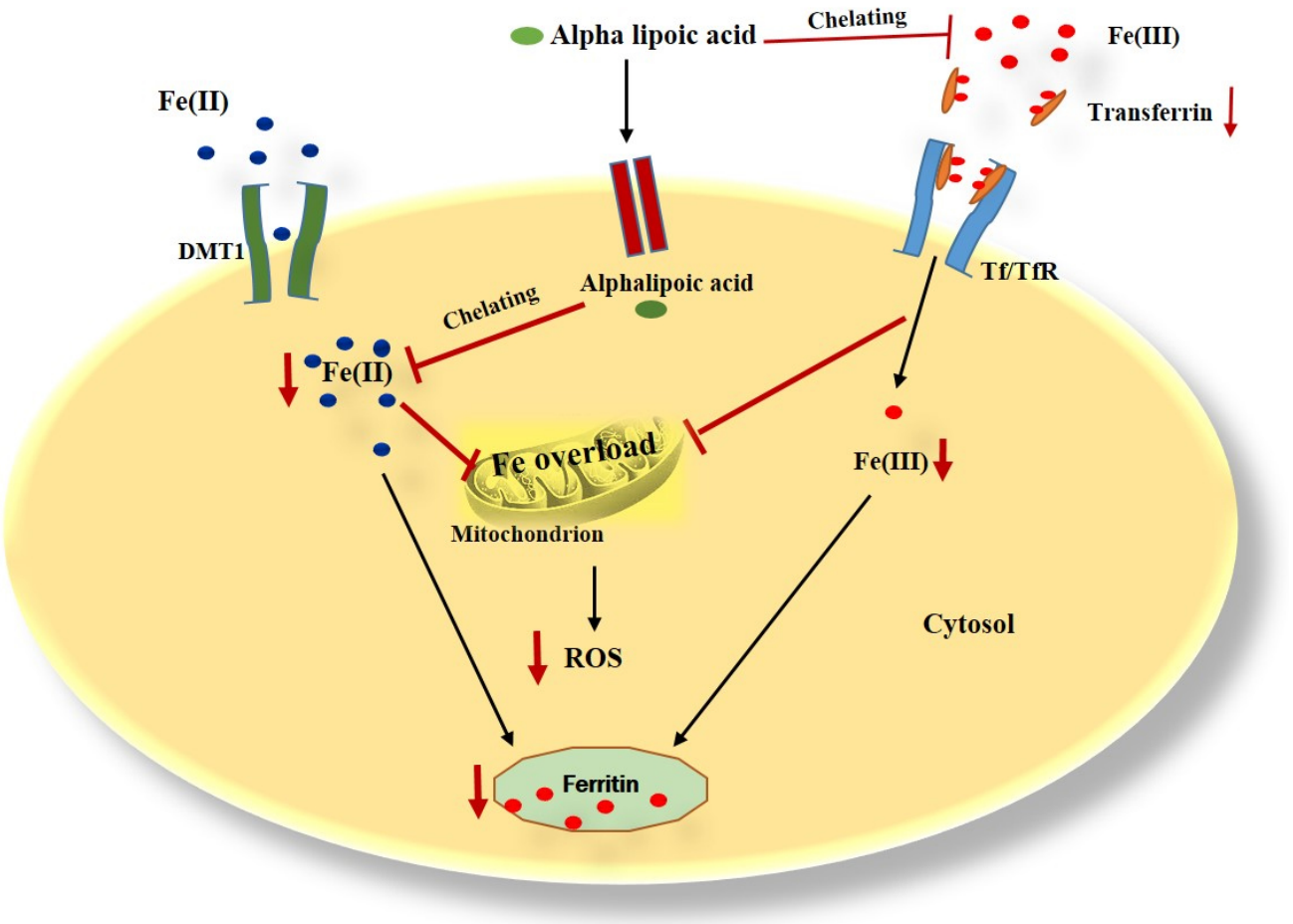

Fig. 6. Cellular mechanism of action of ALA in iron metabolism. Iron can enter cells via various pathways. On the cell membrane, Fe^{3+} is reduced to Fe^{2+} and then absorbed into the cells by Divalent Metal Transporter 1 (DMT1). This process occurs mainly in the duodenal epithelial cell. In plasma Fe^{3+} and transferrin (Tf) bind to the transferrin receptor (TfR) located on the cell membrane and enter the cell by endocytosis. This process is the major source of intracellular iron for most cells. ALA can chelate Fe^{2+} in cells leading to a decrease in cellular concentration of Fe^{2+} iron-induced oxidative stress, and Fe^{2+} storage in the ferritin. Moreover, in plasma, ALA can chelate Fe^{3+} and hinder its binding to Tf, which causes a reduction in Fe^{3+} transfer to the cells by the TfR. This process also can result in reduced cellular concentration of Fe^{3+}, iron overload, iron-induced oxidative stress, and iron storage proteins like ferritin. DMT1, Divalent Metal Transporter 1; ROS, Reactive oxygen species; TfR, Transferrin receptor.

significant role in the development of anemia in patients with chronic conditions such as end-stage renal diseases [7], fatty liver [30], and sickle cell disease [13]. Elevated oxidative stress can influence red blood cell (RBC) membranes, leading to lipid peroxidation and impairing membrane integrity [38]. This, consequently can compromise the structure and function of the hemoglobin within RBCs. Therefore, extended exposure to oxidative stress could potentially reduce the lifespan of RBCs, leading to a decrease in both RBC and hemoglobin levels [39]. As all the studies [7,13,21,27–29,32] in the first subgroup of Hgb were conducted on patients with inflammatory conditions, the increasing effect of ALA on hemoglobin can be related to its reduction effect on oxidative stress and inflammatory factors which consequently protect red blood cell membrane from oxidative damage [13].

However, as the baseline hematological indices were not considered as an inclusion criterion in most of the included studies, interpreting the effect of ALA on hematological indices based on the baseline values is difficult. Therefore, it seems, that to assess the effect of ALA on iron-related parameters, more strength inclusion criteria are needed.

In the blood, iron is mainly bound to transferrin, and TIBC depends on the transferrin concentration. The fraction of transferrin to which iron is not bound is called "unsaturated iron-binding capacity" (UIBC). The TIBC is equal to the sum of serum iron concentration and the UIBC. TIBC can be used as a diagnostic test for both iron deficiency and iron overload [40]. Moreover, TIBC has been reported as a negative acute phase reactant. However, diurnal variation in plasma iron can reduce TIBC diagnostic

value [41]. Combining the results of the four studies revealed that ALA supplementation could non-significantly increase TIBC by 3.95 µ/dL. More evaluation of the studies revealed that our study on thalassemia patients accounted for the major weight of the included studies [32]. Compared to the other studies, the baseline level of TIBC in thalassemia patients was lower. This may be related to the pathologic condition of the patients. As these patients are at higher risk for oxidative stress and inflammation, mainly due to iron overload and blood transfusion, the increasing effect of ALA on TIBC might be related to the lower baseline values of TIBC and also ALA's anti-inflammatory effect, as previously noted. However, considering the small number of studies and the heterogeneity between studies regarding participants' health status, this finding may not be conclusive.

Although the exact mechanism of action of ALA on iron metabolism is not fully detected, the suggested mechanisms for observed findings in this study may be attributed to the chelating effects of ALA and its role as an inhibiting agent of iron uptake [2,11,22]. Hence, it may form insoluble complexes of high affinity, which cannot be released to uptake by the cells, leading to a reduction in serum iron, iron overload, and iron-induced oxidative stress. In fact, some studies indicated that ALA can chelate Fe^{2+} in cells [42,43] leading to a decrease in its cellular concentration. Moreover, in serum ALA chelates Fe^{3+} and hinders its binding to transferrin, leading to reduced Fe^{3+} transportation to the cell by the transferrin receptor (TfR) [43,44]. This process also can result in reduced cellular concentration of Fe^{3+}, iron overload, and iron storage proteins like ferritin (Fig. 6). Besides, ALA can serve as an antioxidant agent and effectively scavenge reactive oxygen species, thereby protecting the RBC from oxidative stress [21,45]. This protective mechanism ultimately can lead to the preservation or elevation of hemoglobin levels, which are otherwise reduced by inflammatory conditions [44]. Hence ALA may hold promises for exerting beneficial effects in anemia induced by inflammation.

The current study has some strengths. The first of which is the inclusion of RCTs assessing the role of ALA supplementation on iron metabolism parameters, allowing us to achieve more coherent and conclusive results. Adopting a comprehensive and robust methodology to identify available studies that assessed the effect of ALA on iron metabolism parameters, performing subgroup analysis to determine the source of heterogeneity, and evaluating the effects of a single study on the overall result represent additional strengths. However, some limitations should be taken into account when interpreting our findings. According to our risk of bias assessment, five of the ten included studies had a poor quality, which may affect the results for overall and subgroup analysis. Additionally, the effect of ALA on iron metabolism parameters may depend on the baseline values, health status of participants, duration of the intervention, dose of ALA, and dietary intake. As most of the included studies did not consider these variables, it is difficult to discern a clear conclusion.

5. Conclusion

The overall results of this systematic review indicated that ALA supplementation had no statistically significant effect on iron homeostasis related parameters including ferritin, serum iron, Hgb, and TIBC when compared to the control group. This may be related to heterogeneity in patients' characteristics and their health status. As the majority of the included studies were conducted on patients suffering from chronic inflammation which affects the response of Iron homeostasis to ALA supplementation. However, the results of the subgroup analysis revealed a significant increasing effect of ALA on Hgb in patients with hematological disorders and in studies with durations longer than 8 weeks. Furthermore, the results of the sensitivity analysis revealed that none of the included studies could affect the overall result. Nevertheless, due to the limited number of available studies, heterogeneity regarding participant's health status, baseline values of variables, and dietary intake, caution should be taken when interpreting the current results. More consistent clinical trials, with larger sample sizes, considering stronger inclusion criteria, are required to better discern the actual effect of ALA supplementation on iron homeostasis.

Availability of Data and Materials

The dataset applied and analyzed for the present study is available from the first author (el_sharifi66@yahoo.com) on a reasonable request.

Author Contributions

ESZ: Contributed to the study design and data collection, and interpretation and drafting the manuscript. HA: Participated in the study conception, revising the paper critically and approving the version of the manuscript being submitted. Both authors contributed to editorial changes in the manuscript. Both authors read and approved the final manuscript. Both authors have participated sufficiently in the work and agreed to be accountable for all aspects of the work.

Ethics Approval and Consent to Participate

Not applicable.

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Conflict of Interest

The authors declare no conflict of interest.

Supplementary Material

Supplementary material associated with this article can be found, in the online version, at https://doi.org/10.31083/IJVNR36623.

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