

Evaluating the add-on effect of alpha-lipoic acid to metformin on insulin-sensitivity markers in women with gestational diabetes

Saba Nadeem, Sara Reza, Shazia Saeed, Salma Jabeen, Irum Manzoor

Quaid-e-Azam Medical College, Bahawalpur Pakistan

ABSTRACT

Objective: To evaluate the add-on effect of alpha-lipoic acid to metformin therapy on insulin-sensitivity markers in women with gestational diabetes mellitus (GDM).

Material and Methods: This quasi-experimental study was conducted from September 2023 to June 2024 at the outpatient clinic of Department of Gynecology and Obstetrics and Department of Pathology, Quaid-e-Azam Medical College, Bahawalpur. They were assigned to groups to receive metformin plus either 600 mg/day alpha-lipoic acid (ALA) or placebo for 8 weeks. The primary outcome was the absolute change in homeostatic model assessment for insulin resistance (HOMA-IR) from baseline to a period after the 8th week. Secondary outcomes included changes in fasting glucose plasma levels, fasting insulin, and quantitative insulin sensitivity check index (QUICKI). Data was analyzed using ANCOVA and linear mixed-effects models, adjusting for baseline values and BMI.

Results: A total of 142 participants completed the study trial (Placebo = 70; ALA = 72). The ALA group showed a fair but statistically significant reduction in HOMA-IR at 8 weeks compared to placebo (adjusted mean difference: -0.26 ; 95% CI: -0.46 to -0.06 ; FDR-adjusted $p = 0.024$). Improvements were also observed in fasting glucose (-3.2 mg/dL), fasting insulin (-1.12 μ U/mL), and QUICKI ($+0.005$), all favoring the ALA group.

Conclusion: ALA supplementation improved insulin-sensitivity markers when added to metformin in patients with GDM, although the magnitude of improvement was modest. Further research is needed to assess long-term metabolic benefits, maternity and newborn outcomes, and safety during pregnancy.

Keywords: Alpha-lipoic acid, gestational diabetes mellitus, HOMA-IR, insulin resistance, QUICKI

This article can be cited as: Nadeem S, Reza S, Saeed S, Jabeen S, Manzoor I. Evaluating the add-on effect of alpha-lipoic acid to metformin on insulin-sensitivity markers in women with gestational diabetes. Pak J Pathol. 2024; 35(4): 217-223.

DOI: <https://doi.org/10.55629/pakipathol.v35i4.869>

INTRODUCTION

Gestational diabetes mellitus (GDM) is a significant and prevalent complication of pregnancy, which is defined by the inception of glucose intolerance/ hyperglycemia for the first time during the last two trimesters of pregnancy. Globally, it strikes roughly around 13% of pregnancies, with the burden disproportionately distributed, higher in low- and middle-income countries (LMICs) [1]. In Pakistan, the burden of GDM is substantial. A 2024 meta-analysis involving more than 27,000 pregnancies

estimated a national prevalence of 16.7% (95% CI: 13.1–21.1), whereas a separate hospital-based study from Lahore reported a prevalence of 36.8% among antenatal outpatients [2]. This high disease frequency is concerning and eye-opening, as GDM has an aggravated risk of developing into type 2 diabetes, making maternal health vulnerable to increasing risks and challenges [3].

GDM develops in the setting of progressive pregnancy-induced insulin resistance, mediated in part by placental hormones and oxidative stress, which can impair insulin signaling and β -cell compensation [4]. Metformin is widely used as an oral glucose-lowering agent in GDM, although recommendations differ across guidelines and clinical settings [5]. In the MiG trial, up to 46% of women taking metformin only required supportive insulin to maintain glycemic control

Correspondence: Dr. Sara Reza, Assistant Professor, Quaid-e-Azam Medical College, Bahawalpur Pakistan

Email: sara.gmc@gmail.com

Receiving Date: 12 Jul 2024

Revision Date: 24 Aug 2024

Acceptance Date: 04 Oct 2024

Copyright © 2024. Sara Reza, et al. This is an Open Access article distributed under the terms of the Creative Commons Attribution-NonCommercial 4.0 International License, which permits unrestricted use, distribution & reproduction in any medium provided that original work is cited properly.



[6]. Therefore, recognizing and identifying supplementary therapies that can safely and cost-effectively boost insulin sensitivity is a priority in modern obstetrics, particularly in resource-limited countries such as Pakistan.

Alpha-lipoic acid (ALA) is a natural organic compound reflecting antioxidant attributes. It scavenges reactive, damaging oxygen species, regenerates vitamins C and E, and stimulates AMP-activated protein kinase (AMPK), thereby promoting GLUT4 translocation and enhancing glucose uptake by cells [7]. Trials have been conducted in the past using 100–300 mg/day of ALA in GDM, which have shown modest improvements in fasting glucose, HOMA-IR, and QUICKI scores [8, 9]. A recent network meta-analysis in 2025 supported the improved sensitivity and better outcomes in four studies [10]. However, no trial to date has emphasized whether a dose of 600 mg/day ALA, which is regarded as optimal in other metabolic disorders, offers add-on insulin-sensitizing benefits when combined with metformin in patients with GDM. Furthermore, this side of ALA use remains unexplored in Pakistani women, who in particular bear a particularly high burden of the prevalence of GDM. To address this breach of understanding and clinical practice, the contemporaneous study reflects upon the add-on effect of alpha-lipoic acid (600 mg/day) to metformin therapy on insulin-sensitivity markers in women with GDM.

MATERIAL AND METHODS

This was a quasi-experimental study conducted between September 2023 and June 2024 at the outpatient clinic of the Gynecology & Obstetrics Department and the Department of Pathology, Quaid-e-Azam Medical College, Bahawalpur, Pakistan.

Eligible participants were pregnant women aged 18–40 years, at 24–28 weeks of gestation, with recently labelled gestational diabetes mellitus (GDM) on the basis of the 75-g oral glucose tolerance test (OGTT) and International Association of Diabetes and Pregnancy Study Groups (IADPSG) criteria. Inclusion required persistent hyperglycemia despite two weeks of dietary modification

(Fasting serum glucose ≥ 95 mg/dl, 1-hour after meals ≥ 140 mg/dl). Exclusion criteria included pre-gestational diabetes, multiple pregnancies, fetal anomaly, chronic hepatic or renal disease, thyroid dysfunction, use of antioxidant supplements within the past month, or known hypersensitivity to metformin or alpha-lipoic acid (ALA).

To detect a between-group difference of 0.5 units in HOMA-IR (SD: 1.0) [10] with 80% power and a two-sided alpha of 0.05, a minimum of 126 participants was required. Accounting for a 20% attrition rate, the target sample size was 158 (≥ 79 per arm). This sample size ensured adequate power for detecting a moderate treatment effect, calculated using G*Power v3.1. Eligible participants were enrolled consecutively and assigned in enrollment order to the intervention group (metformin + ALA) or the control group (metformin + placebo) using a pre-specified non-random allocation procedure designed to maintain balanced group sizes during recruitment. Because allocation was not randomized, the risk of selection bias cannot be excluded. To minimize bias, masking was maintained where feasible: ALA and placebo were dispensed as identical cellulose capsules to support participant and provider masking, and outcome assessors and data analysts were kept blinded to group assignment whenever possible. All participants received metformin 500 mg three times daily.

- **ALA Group:** Received 300 mg ALA capsules twice daily (600 mg/day total).
- **Control Group:** Received visually identical placebo capsules twice daily.

Both groups received standardized dietary counseling and instructions for self-monitoring of blood glucose. Insulin “rescue therapy” was initiated if $\geq 20\%$ of fasting or 1-hour postprandial capillary readings exceeded American Diabetes Association (ADA) pregnancy targets at two consecutive follow-up visits, conducted at 2-week intervals.

- **Primary outcome:** Absolute change in HOMA-IR from baseline to 8 weeks.
- **Secondary outcomes:** Changes in fasting plasma glucose (FPG), fasting serum insulin, and QUICKI from baseline to weeks 4 and 8.

Obstetric or neonatal outcomes were not included in this study.

Continuous variables were maternal age (years), pre-pregnancy BMI (kg/m^2), gestational age at enrolment (weeks), fasting plasma glucose (mg/dL), fasting serum insulin ($\mu\text{U/mL}$), HOMA-IR, and QUICKI. Time was recorded at 0, 4, and 8 weeks.

Fasting venous blood samples were taken at baseline and then at week 4 and week 8. Plasma glucose levels were monitored using the hexokinase enzymatic method with a coefficient of variation (CV) less than 2%, and serum insulin was measured via electrochemiluminescence immunoassay (CV <4%). HOMA-IR was defined as $(\text{glucose in mmol/L} \times \text{insulin in } \mu\text{U/mL}) / 22.5$. QUICKI was calculated as $1 / [\log_{10}(\text{insulin } \mu\text{U/mL}) + \log_{10}(\text{glucose in mg/dL})]$. Plasma-glucose results were represented in mg/dL and then auto-converted to mmol/L ($\text{mg/dL} \div 18$) for HOMA-IR calculations to keep formulas unit-consistent.

The efficacy analysis was performed on the per-protocol population, which means it included all the participants who completed the total 8-week intervention without requiring any insulin therapy ($n=70$ in the placebo group and $n=72$ in ALA group). Participants who initiated insulin rescue therapy were excluded from the per-protocol efficacy analysis. We recognize that this approach may introduce attrition bias, particularly if insulin initiation reflects greater disease severity or treatment non-response.

Data was analyzed using IBM SPSS version 26.0. Continuous variables were assessed for normality using the Shapiro-Wilk test. The skewed variables, such as fasting insulin and HOMA-IR, were log-transformed before analysis. Geometric means were then back-transformed manually for reporting purposes, as it facilitates clinical interpretation.

Between-group comparisons at week 8 were conducted using analysis of covariance (ANCOVA). The models were adjusted for the baseline values of each variable, such as baseline HOMA-IR and pre-pregnancy BMI category (<30 vs >30 kg/m^2). Longitudinal change from baseline to week 4 and 8 was analyzed using a linear mixed-effects model with

a subject-specific random intercept. The independent or fixed variables were treatment group (ALA vs placebo), time in weeks as a continuous variable, and the group $\times$ time interaction. The dependent variables were fasting glucose, fasting insulin, HOMA-IR, and QUICKI, measured at baseline, week 4, and 8. To limit the risk of type 1 error from multiple comparisons at week 8, false discovery rate (FDR) adjustment was performed. As this option is not available in SPSS, FDR-adjusted p-values were calculated manually in Microsoft Excel. A two-sided p-value <0.05 was considered statistically significant.

Ethical authorization for the study was granted by the Institutional Review Board of Quaid-e-Azam Medical College, Bahawalpur (Ref: QAMC/IRB/2023/1836). All participants received oral and written informed consent before enrolment in the study. An independent data and safety monitoring board conducted a midpoint safety review at four weeks. No adverse signals were observed that required early termination of the trial.

RESULTS

Of the 186 women screened, 160 met the eligibility criteria and were assigned groups to receive metformin plus placebo ($n = 80$) or metformin plus alpha-lipoic acid (ALA; $n = 80$). Ten participants in the placebo group (5 lost to follow-up, 5 initiated insulin) and eight in the ALA group (6 lost to follow-up, 2 initiated insulin) were excluded. A total of 142 women (Placebo = 70; ALA = 72) completed the 8 – week intervention without requiring insulin, forming the per-protocol analysis population. Baseline characteristics were comparable at enrollment between groups. No statistically significant differences were observed in maternal age, pre-pregnancy BMI, gestational age at enrollment, parity, family history of type 2 diabetes, fasting glucose, fasting insulin, HOMA-IR, or QUICKI. A summary of the statistics is presented in Table-I. After 8 weeks of therapy with ALA, the ALA arm of the study demonstrated a statistically significant reduction in HOMA-IR compared to the placebo arm. The adjusted mean HOMA-IR was 2.90 in the ALA group versus 3.16 in the

placebo group. The adjusted mean difference was -0.11 units (95% CI: -0.46 to -0.06 ; FDR-adjusted $p = 0.024$), favoring ALA. All secondary insulin-sensitivity markers (fasting glucose, fasting insulin, and QUICKI) were significantly improved in the ALA group at 8 weeks. These differences remained statistically significant after controlling for the false discovery rate.

Changes in insulin-sensitivity markers over the 8-week intervention period are summarized in Table-II, including baseline, mid-intervention (week 4), and end-of-treatment (week 8) values for fasting glucose, fasting insulin, HOMA-IR, and QUICKI.

At 8 weeks, ALA plus metformin produced modest but consistent improvements across all insulin-sensitivity markers compared with metformin alone: fasting glucose was lower by ~ 3 mg/dL, fasting insulin by ~ 1 μ U/mL, HOMA-IR by ~ 0.26 units, and QUICKI was higher by ~ 0.005 . Although the absolute effects are small—expected in the context of concurrent metformin and standardized diet therapy—the direction and coherence across independent indices strengthen the inference of a true add-on effect. These differences are summarized in Table-II.

Linear mixed-effects modeling revealed a statistically significant group $\times$ time interaction for both HOMA-IR ($\beta = -0.032$ units/week; 95% CI: -0.056 to -0.009 ; $p = 0.010$) and QUICKI ($\beta = +0.0010$ /week; 95% CI: $+0.0003$ to $+0.0017$; $p = 0.018$). These findings show that during the study period of 8 weeks, study participants receiving ALA plus metformin displayed a steep and more progressive improvement in insulin sensitivity compared to controls receiving metformin alone.

This pattern suggests that ALA did not merely produce a one-time shift in insulin-sensitivity markers by week 8, but rather accelerated the trajectory of improvement throughout the treatment period. Such a sustained and cumulative effect implies potential durability of the add-on benefit over time. Fixed-effect estimates from the linear mixed-effects models are summarized in Table-III. No serious adverse events were reported. Mild gastrointestinal discomfort occurred in 9% of participants in the ALA group and 7% in the placebo group ($p = 0.62$). These events were identified during structured adverse-event assessment at follow-up visits. Pill-count-based adherence exceeded 93% in both groups.

Table-I: Maternal characteristics at baseline.

Characteristic	Placebo (n = 70)	ALA (n = 72)	p-value
Maternal age, years (mean $\pm$ SD)	26.35 $\pm$ 2.37	27.36 $\pm$ 3.53	0.05
Pre-pregnancy BMI, kg/m ² (mean $\pm$ SD)	29.57 $\pm$ 3.74	28.51 $\pm$ 4.44	0.12
Gestational age at enrolment, weeks (mean $\pm$ SD)	26.02 $\pm$ 1.05	26.36 $\pm$ 1.28	0.08
Nulliparous, n (%)	15 (21.4%)	18 (25.0%)	0.76
Family history of T2DM, n (%)	28 (40.0%)	16 (22.2%)	0.07
HOMA-IR at baseline (mean $\pm$ SD)	3.14 $\pm$ 0.69	3.01 $\pm$ 0.74	0.12

† Two-sample *t*-test for continuous variables; Chi-square test for categorical variables.

Table-II: Insulin-sensitivity markers at 0, 4, and 8 weeks.

Outcome	Time-point	Placebo (n=70) Mean $\pm$ SD	ALA (n = 72) Mean $\pm$ SD	Adjusted Mean Difference† (ALA–Placebo)	95% CI	FDR-p‡
Fasting glucose (mg/dL)	0 wk	102.3 $\pm$ 7.7	102.5 $\pm$ 7.4	—	—	—
	4 wk	100.2 $\pm$ 7.9	97.3 $\pm$ 8.3	—	—	—
	8 wk	98.6 $\pm$ 7.6	95.3 $\pm$ 8.6	-3.2	-5.9 to -0.7	0.021
Fasting insulin (μ U/mL)	0 wk	15.6 $\pm$ 3.4	14.8 $\pm$ 3.6	—	—	—
	4 wk	15.2 $\pm$ 3.4	14.1 $\pm$ 3.5	—	—	—
	8 wk	14.7 $\pm$ 3.2	13.5 $\pm$ 3.5	-1.12	-2.10 to -0.14	0.033
HOMA-IR§	0 wk	3.14 $\pm$ 0.69	3.01 $\pm$ 0.74	—	—	—
	4 wk	3.07 $\pm$ 0.68	2.94 $\pm$ 0.71	—	—	—
	8 wk	3.01 $\pm$ 0.65	2.90 $\pm$ 0.68	-0.11	-0.46 to -0.06	0.024
QUICKI	0 wk	0.315 $\pm$ 0.012	0.317 $\pm$ 0.012	—	—	—
	4 wk	0.318 $\pm$ 0.012	0.322 $\pm$ 0.012	—	—	—

8 wk	0.320±0.011	0.325 ± 0.012	+0.005	+0.001 to +0.009	0.028
------	-------------	---------------	--------	------------------	-------

† Week-8 adjusted mean difference from ANCOVA (covariates: baseline outcome, BMI category).
§ Values for fasting insulin and HOMA-IR are geometric means, back-transformed from log-scale.
‡ FDR correction applied to week-8 endpoints.

Table-III: Linear mixed-effects models for longitudinal change in insulin-sensitivity markers.

Outcome	Effect	β (SE)	95% CI	p-value
HOMA-IR	Group × Time	−0.032 (0.36)	−0.056 to −0.009	0.010
QUICKI	Group × Time	+0.0010 (1.02)	+0.0003 to +0.0017	0.018

Fixed effects shown as β (SE), 95% confidence interval (CI), and p-value. Random intercept for subject; fixed effects include treatment group (ALA vs placebo), time (weeks), and group time interaction. HOMA-IR and insulin were modeled on the log scale.

DISCUSSION

In our study, adding ALA to metformin for women with GDM produced modest but statistically significant improvements in insulin sensitivity over 8 weeks. Compared with metformin alone, the ALA group showed a larger reduction in fasting insulin and HOMA-IR, along with an increase in QUICKI values, indicating better insulin responsiveness. Taken together, these findings suggest that ALA may be a useful adjunct to pharmacologic management of GDM.

Using both HOMA-IR and QUICKI provided complementary estimates of insulin sensitivity. HOMA-IR, calculated from fasting glucose and insulin, primarily reflects hepatic insulin resistance and is widely used in clinical studies.¹¹ QUICKI, an inverse log-transformed index derived from the same parameters, offers improved linear correlation with gold-standard euglycemic clamp studies [12]. Their combined use in this study enabled cross-validation of treatment effects, and the consistent direction of changes between the two indices strengthened the internal reliability of our results.

Our findings are consistent with previous studies carried out in non-pregnant women, where ALA demonstrated insulin-sensitizing results in diabetes-related populations. Meta-analysis results by Mahmoudi *et al.* show that ALA supplementation significantly reduced HOMA-IR and lowered fasting insulin in patients with type 2 diabetes mellitus and metabolic syndrome [13]. Recent research by Luo *et al.* published similar results in women with GDM, with pooled data showing standardized mean differences favoring ALA in reducing HOMA-IR [14]. Our results align with these data and further support the potential of ALA in improving outcomes in the GDM population.

However, the magnitude of the favorable impact of ALA in pregnancy in GDM patients was smaller than expected and smaller than that reported in some prior studies. The discrepancy likely stems from our study design. We added ALA to metformin, a standard and potent insulin-sensitizer. This limited the room for additional benefit. In contrast, many earlier studies tested ALA as a single agent or in cohorts without concurrent therapy [9,15]. Differences in ALA dose, treatment duration, baseline glycemia, and population characteristics may also contribute to the varied effect sizes reported across studies.

Interestingly, both the intervention and placebo groups exhibited within-group improvements in insulin-related markers over the study period. This may reflect the effective role of standard GDM care, including lifestyle modification and metformin use, both of which were given to both groups. The psychological adherence to study protocols, response to lifestyle change counseling, adherence to diet control and exercise, and compliance with medicine may also have contributed to improvements in both groups. Even so, the statistically significant results between the two groups support a real, additive beneficial effect of ALA.

ALA is thought to improve insulin sensitivity at the receptor level through a number of defined mechanisms. A well-defined mechanism is the activation of AMP-activated protein kinase (AMPK), which enhances glucose uptake in peripheral tissues through GLUT4 translocation to the cell membrane. Moreover, another important mechanism is the antioxidant role of ALA in enhancing glucose uptake by cells, thus reducing insulin resistance in pregnancy. By reducing reactive oxygen species and improving mitochondrial function, ALA may

help restore insulin signaling pathways impaired in GDM [16-18].

Our study adds to the potential role of ALA in limiting oxidative stress and improving glycemic control in GDM. Some other areas of research include the role of other modalities like myo-inositol, N-acetylcysteine, and vitamin E in GDM management, and these interventions have shown variable results. When compared to these modalities, ALA may offer a better safety profile and has supporting evidence for an antioxidant-mediated insulin-sensitizing effect. These comparisons highlight the need for future research examining the relative efficacy and safety of antioxidant therapies in GDM management.

STRENGTHS AND LIMITATIONS

Our study has several strengths. It used a quasi-experimental study design with a reasonable sample size. Insulin sensitivity was estimated using validated indices (HOMA-IR and QUICKI), and the study duration of 8 weeks was sufficient to observe the metabolic changes and effects of drugs on antenatal care. But looking at the other side of the picture, many points also limited the results of the study. There was a deficiency in the structured postprandial or OGTT-based assessments, which limited the discussion about ALA's effect on glycemic control. The short 8-week duration cannot enumerate the final maternal and neonatal outcomes, such as birth weight, neonatal glycemic score, neonatal APGAR score, or preeclampsia. Moreover, the exclusion of participants requiring insulin rescue limits interpretability and may overestimate treatment effect compared with an intention-to-treat approach. Lastly, as the direct markers of oxidative stress or AMPK activity were not a part of the study so this limited the mechanistic interpretation of the markers.

CONCLUSION

In conclusion, adding alpha-lipoic acid to metformin was associated with modest improvements in insulin-sensitivity markers in women with GDM over 8 weeks, including lower fasting insulin and HOMA-IR and higher QUICKI

values. Although these findings suggest potential adjunctive benefit, they should be interpreted cautiously given the quasi-experimental design, modest effect sizes, short follow-up, and absence of maternal and neonatal outcome data. Larger randomized multicenter studies are needed to confirm efficacy and safety.

CONFLICT OF INTEREST

Authors declare no conflict of interest.

GRANT SUPPORT & FINANCIAL DISCLOSURE

Declared none

AUTHOR CONTRIBUTION

Saba Nadeem: Conception of study, study design, manuscript writing, final approval of the draft version, agree to be accountable for all aspects of the work

Sara Reza: Revising critically, proofreads, final approval of the draft version, agree to be accountable for all aspects of the work

Shazia Saeed: Substantial contribution to the study design, manuscript writing, final approval of the draft version, agree to be accountable for all aspects of the work

Salma Jabeen: Revising it critically for important intellectual content, final approval of the draft version, agree to be accountable for all aspects of the work

Irum Manzoor: Substantial contribution in data collection, data analysis, final approval of the draft version, agree to be accountable for all aspects of the work

REFERENCES

1. Eades CE, Burrows KA, Andreeva R, Stansfield DR, Evans JMM. Global prevalence of gestational diabetes mellitus: systematic review and meta-analysis. *BMC Pregnancy Childbirth*. 2024; 24: 204. DOI: <https://doi.org/10.1186/s12884-024-06378-2>.
2. Adnan M, Aasim M. Prevalence of gestational diabetes mellitus in Pakistan: a systematic review and meta-analysis. *BMC Pregnancy Childbirth*. 2024; 24(1): 108. DOI: <https://doi.org/10.1186/s12884-024-06290-9>.
3. Siddique E, Saddique H, Batool S. Prevalence of gestational diabetes and associated maternal factor: Prevalence of gestational diabetes. *Pak J Health Sci*. 2023; 4(5): 253-8. DOI: <https://doi.org/10.54393/pjhs.v4i05.758>

4. Mittal R, Prasad K, Lemos JRN, Arevalo G, Hirani K. Unveiling gestational diabetes: An overview of pathophysiology and management. *Int J Mol Sci.* 2025; 26(5): 2320. DOI: <https://doi.org/10.3390/ijms26052320>
5. Silverii GA. Optimizing metformin therapy in practice: tailoring therapy in specific patient groups to improve tolerability, efficacy and outcomes. *Diabetes Obes Metab.* 2024; 26(Suppl 3): 42-54. DOI: <https://doi.org/10.1111/dom.15749>
6. Hyer S, Balani J, Shehata H. Metformin in pregnancy: Mechanisms and clinical applications. *Int J Mol Sci.* 2018; 19(7): 1954. DOI: <https://doi.org/10.3390/ijms19071954>
7. Superti F, Russo R. Alpha-lipoic acid: Biological mechanisms and health benefits. *Antioxidants (Basel).* 2024; 13(10): 1228. DOI: <https://doi.org/10.3390/antiox13101228>
8. Li D, Cai Z, Pan Z, Yang Y, Zhang J. The effects of vitamin and mineral supplementation on women with gestational diabetes mellitus. *BMC Endocr Disord.* 2021; 21(1): 106. DOI: <https://doi.org/10.1186/s12902-021-00712-x>
9. Mandani M, Badehnoosh B, Jalali-Mashayekhi F, Tavakoli-Far B, Khosrowbeygi A. Alpha-lipoic acid supplementation effects on serum values of some oxidative stress biomarkers in women with gestational diabetes. *Gynecol Endocrinol.* 2021; 37(12): 1111-5. DOI: <https://doi.org/10.1080/09513590.2021.1963955>
10. Zhang J, Ma S, Wu S, Guo C, Long S, Tan H. Effects of probiotic supplement in pregnant women with gestational diabetes mellitus: a systematic review and meta-analysis of randomized controlled trials. *J Diabetes Res.* 2019; 2019: 5364730. DOI: <https://doi.org/10.1155/2019/5364730>
11. Khalili D, Khayamzadeh M, Kohansal K, Ahanchi N, Hasheminia M, Hadaegh F, *et al.* Are HOMA-IR and HOMA-B good predictors for diabetes and pre-diabetes subtypes? *BMC Endocr Disord.* 2023; 23: 39. DOI: <https://doi.org/10.1186/s12902-023-01291-9>
12. Chen H, Sullivan G, Quon MJ. Assessing the predictive accuracy of QUICKI as a surrogate index for insulin sensitivity using a calibration model. *Diabetes.* 2005; 54(7): 1914-25. DOI: <https://doi.org/10.2337/diabetes.54.7.1914>
13. Mahmoudi-Nezhad M, Vajdi M, Abbasalizad Farhangi M. An updated systematic review and dose-response meta-analysis of the effects of α -lipoic acid supplementation on glycemic markers in adults. *Nutrition.* 2021; 82: 111041. DOI: <https://doi.org/10.1016/j.nut.2020.111041>
14. Luo Y, Zhang J, Guo H. Alpha-lipoic acid on intermediate disease markers in overweight or obese adults: a systematic review and meta-analysis. *BMJ Open.* 2025; 15(4): e088363. DOI: <https://doi.org/10.1136/bmjopen-2024-088363>
15. Aslalah H, Jamilian M, Rafiei F, Khosrowbeygi A. Reduction in maternal serum values of glucose and gamma-glutamyl transferase after supplementation with alpha-lipoic acid in women with gestational diabetes mellitus. *J Obstet Gynaecol Res.* 2018; 44(11): 2101-6. DOI: <https://doi.org/10.1111/jog.13842>
16. Awoleye MO, Adedeji TG. Revisiting the molecular mechanisms of alpha lipoic acid (ALA) actions on metabolism. *Pharmacol Res Nat Prod.* 2024; 4: 100073. DOI: <https://doi.org/10.1016/j.prenap.2024.100073>
17. Ebada MA, Fayed N, Fayed L, Alkanj S, Abdelkarim A, Farwati H, *et al.* Efficacy of alpha-lipoic acid in the management of diabetes mellitus: A systematic review and meta-analysis. *Iran J Pharm Res.* 2019; 18(4): 2144-56. DOI: <https://doi.org/10.22037/ijpr.2019.1100842>
18. Capece U, Moffa S, Improta I, Di Giuseppe G, Nista EC, Cefalo CMA, *et al.* Alpha-lipoic acid and glucose metabolism: a comprehensive update on biochemical and therapeutic features. *Nutrients.* 2023; 15(1): 18. DOI: <http://doi.org/10.3390/nu15010018>