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Article

Exploring the Efficacy of Alpha-Lipoic Acid in Comorbid Osteoarthritis and Type 2 Diabetes Mellitus

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Abstract: The comorbidity of osteoarthritis and type 2 diabetes mellitus represents a complex clinical challenge and complicates patient management due to the interplay of overlapping pathophysiological mechanisms. The research aimed to analyze the exacerbation of clinical symptoms and biochemical markers in patients with osteoarthritis and type 2 diabetes mellitus compared to those with osteoarthritis. We utilized various assessment methods to measure the patient cohorts' inflammation, oxidative stress, and glycemic control. The study also involved the administration of alpha-lipoic acid to patients with comorbid osteoarthritis and type 2 diabetes mellitus and monitored its effects on joint function, inflammatory markers, oxidative stress levels, and glycemic control. Our findings revealed that the presence of type 2 diabetes mellitus significantly intensified osteoarthritis symptoms and altered biochemical markers, including increased inflammation, elevated oxidative stress, and disrupted immunological balance. The treatment with alpha-lipoic acid resulted in improved joint function, reduced inflammation and oxidative stress levels, and better glycemic control. Additionally, it was identified several potential predictors for developing osteoarthritis and type 2 diabetes mellitus comorbidity. The results underscore the detrimental impact of type 2 diabetes mellitus on osteoarthritis and highlight the beneficial effects of alpha-lipoic acid in alleviating some of the adverse consequences associated with this comorbidity. Nonetheless, further research is necessary to comprehensively evaluate the therapeutic efficacy of alpha-lipoic acid and its long-term effects on managing comorbidity of osteoarthritis and type 2 diabetes mellitus.

Keywords: osteoarthritis; type 2 diabetes; diabetes mellitus; alpha-lipoic acid; inflammation; oxidative stress; glycemic control; comorbidity

1. Introduction

With a global prevalence of nearly 23%, osteoarthritis (OA) imposes a significant disease burden, exacerbated by the lack of effective disease-modifying treatments [1–2]. Affecting over 240 million people globally, OA is a major contributor to activity limitation among adults. The pathogenesis of OA remains poorly understood, leading to a lack of effective clinical treatments [3]. Disruptions in glucose metabolism have been shown to cause chondrocyte hypertrophy and extracellular matrix degradation, playing a significant role in the onset and progression of the disease [4]. OA is a degenerative joint disorder that primarily targets the articular cartilage and is influenced by factors such as trauma, metabolic processes, and comorbidities. The ensuing chronic inflammation affects not only the cartilage but also adjacent tissues, further impairing function and exacerbating OA symptoms [5]. The prevalence of osteoarthritis rises with age, and its histological and pathophysiological characteristics indicate an underlying inflammatory process [6]. OA and diabetes mellitus (DM) are both prevalent chronic disorders with long-term detrimental effects. The

pathophysiology of OA is significantly influenced by DM and its associated factors, including hyperglycemia [7].

DM is a significant chronic condition characterized by inadequate insulin production or the body's inability to effectively use insulin, leading to a long-term metabolic disorder [8]. Currently, it affects approximately 537 million adults worldwide, or 10.5% of those aged 20 to 79. Projections indicate that this number will rise to 643 million by 2030 and reach 783 million by 2045 [9]. Several risk factors, such as severe obesity, a family history of diabetes, certain ethnic backgrounds, maternal diabetes or gestational diabetes, and being female, contribute to the earlier onset of type 2 diabetes mellitus (T2DM) [8,10]. Pathogenetically, the primary mechanism involves impaired insulin secretion, coupled with insulin resistance related to ectopic fat accumulation [11–12]. The comorbidity of T2DM and OA is quite common, given that both conditions are prevalent metabolic diseases sharing risk factors such as obesity and aging. Despite this frequent coexistence, there is no clear consensus regarding the direct impact of T2DM on the development and progression of OA. Research findings have been inconsistent, with some studies demonstrating a significant influence of DM on OA, while others have found no substantial link between the two conditions [13–14]. Alpha-lipoic acid (ALA) is used in the comprehensive management of diabetes mellitus due to its antioxidant and pro-oxidant properties that affect insulin sensitivity and secretion [15]. It is widely prescribed for diabetic polyneuropathy, where it enhances nerve conduction and alleviates symptoms. Furthermore, ALA is also utilized in the treatment of other insulin resistance conditions, such as metabolic syndrome, polycystic ovary syndrome, and obesity [16–18]. Studies show that ALA significantly benefits the management of osteoarthritis in patients with DM [19–21]. The use of ALA for managing patients with comorbid osteoarthritis and type 2 diabetes mellitus requires further exploration. Continued research is essential to elucidate its effectiveness and potential advantages in this particular cohort.

2. Materials and Methods

2.1. Sample Collection

Participants for this study were recruited from the Ternopil City Communal Institution "Center for Primary Medical and Sanitary Care" between 2020 and 2023. The research adhered to the core principles set forth in the Council of Europe's Convention on Human Rights and Biomedicine and was conducted in accordance with the ethical guidelines specified in the Declaration of Helsinki by the World Medical Association, including any subsequent revisions. Additionally, the study complied with Ministry of Health of Ukraine Order No. 690 dated September 23, 2009. Informed consent was obtained from all participants prior to their involvement. The study received ethical approval from the Bioethics Committee of I. Horbachevsky Ternopil National Medical University Ministry of Health of Ukraine (Protocol No. 75, November 1, 2023).

The study cohort comprised individuals of Ukrainian ethnicity with European ancestry, aged between 29 and 78 years.

The study involved 123 patients, who were categorized according to the specific pathology under investigation and the presence of comorbidities. The first group consisted of 52 patients diagnosed with OA, while the second group comprised 71 patients with concurrent OA and T2DM. No notable variations in gender, age, or the duration of OA were detected in the study groups (Table 1).

Table 1. Age, gender characteristics, and duration of OA in patients included in the study.

	OA (n=52)	OA+T2DM (n=71)	p ^a -value
Male	53.8%	54.9%	p = 0.7521
Female	46.2%	45.1%	
Age	47 (37.75–52.25)	48 (36–53.75)	p = 0.6143

Duration of OA	7 (5.5–9)	8 (5.0–9.5)	$p = 0.1157$
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Median and interquartile range (IQR) were used to summarize the data. ^a Mann–Whitney ^b.

The cohort of patients with OA and T2DM was subsequently divided according to the treatment regimen: one group without ALA ($n=37$) and another group with ALA ($n=34$). No significant differences in gender, age, duration of OA, or duration of T2DM were observed among the study groups (Table 2).

Table 2. Age, gender characteristics, and duration of OA and T2DM in patients included in the study based on the utilization of ALA in treatment.

	Group without ALA (n=37)	Group with ALA (n=34)	p^a -value
Male	56.8%	52.9%	$p = 0.3472$
Female	46.2%	47.1%	
Age	47.5 (36.5–53)	48 (35.75–54)	$p = 0.7981$
Duration of OA	7.5 (5.0–8.5)	8 (5.25–9.75)	$p = 0.2873$
Duration of T2DM	6.5 (4.0–7.75)	6 (4.25–8)	$p = 0.5428$

Median and interquartile range (IQR) were used to summarize the data. ^a Mann–Whitney ^b.

The group not receiving ALA was treated according to standard protocols, which included a regimen of basic therapy medications, such as nonsteroidal anti-inflammatory drugs, chondroprotectors, and oral hypoglycemic agents (metformin). The group receiving ALA, in addition to the basic therapy regimen, was administered the alpha-lipoic acid by oral administration at a dose of 600 mg once daily for 6 weeks. The levels of the assessed parameters were measured before treatment and after 6 weeks.

Inclusion criteria for the study encompassed individuals of both genders who had a confirmed diagnosis of hip and knee osteoarthritis (ICD-10 codes M16 and M17) and type 2 diabetes mellitus (ICD-10 code E11). Exclusion criteria included: type I diabetes mellitus; thyroid gland disorders, decompensated heart-lung diseases, , acute myocardial infarction; stage II-III hypertension, arrhythmias, unstable ischemic heart diseaserecent, major surgery within the past month; stage III-V chronic kidney disease; use of systemic glucocorticosteroids; severe exhaustion, pregnancy, suspected malignant tumors, infectious and parasitic diseases, congenital anomalies and chromosomal disorders, bleeding tendencies, psychiatric and behavioral disorders, and refusal to participate in the study.

The diagnosis of OA was made based on international guidelines [22]. The assessment of the radiological stages of OA were classified according to the system developed by J.H. Kellgren and J.S. Lawrence, with magnetic resonance imaging (MRI) findings also incorporated into the analysis. The diagnosis of T2DM was confirmed in accordance with international standards [23].

2.2. Laboratory and Clinical Data

In assessing joint status in individuals with OA, the Western Ontario and McMaster Universities Osteoarthritis Index (WOMAC) was utilized as a key evaluation tool [24]. To gauge the severity of OA within the study cohort, the Lequesne Algofunctional Index was applied [24]. Additionally, the Visual Analog Scale (VAS) was used to measure rest pain, movement pain, inflammation and joint dysfunction [25]. The Arthritis Impact Measurement Scales (AIMS) were employed to assess the effect of arthritis on patients' physical and emotional health, measuring multiple dimensions such as Physical Function (FF), Pain (P), Social Function (SF), Emotional Health (EH), General Health Perception (GHP) [26].

Fasting blood glucose levels were measured using automated glucose oxidase methods, while C-peptide levels were analyzed via enzyme-linked immunosorbent assay (ELISA) (BIOSERV Diagnostics GmbH (Germany)). HOMA-IR was calculated from fasting insulin and glucose levels determined by chemiluminescent immunoassay, and Hemoglobin A1c (HbA1c) levels were assessed using high-performance liquid chromatography (HPLC).

The Diabetes Distress Scale (DDS-17) was used to evaluate various dimensions of distress related to diabetes management, including emotional burden (DDS-17-EB), physician-related distress (DDS-17-PRD), regimen-related distress (DDS-17-RRD), and interpersonal distress (DDS-17-ID) and Total DDS-17 score [27]. Additionally, the Problem Areas in Diabetes (PAID) scale assessed overall emotional distress associated with diabetes through a self-administered questionnaire [28].

Leukocytes, neutrophils, and lymphocytes were quantified using automated complete blood count (CBC) analyzers. The neutrophil-to-lymphocyte ratio (NLR) was calculated from these CBC results. C-Reactive Protein (CRP) levels were measured with ELISA (BIOSERV Diagnostics GmbH (Germany)). Hydroxyproline and malondialdehyde (MA) were quantified using colorimetric assays and thiobarbituric acid reactive substances (TBARS) assays. Ceruloplasmin, α_1 -antitrypsin and α_2 -Macroglobulin levels were determined using nephelometry or ELISA (BIOSERV Diagnostics GmbH (Germany)), while kallikrein levels were assessed through enzyme immunoassays. Superoxide dismutase (SOD) and catalase activities were measured using colorimetric and spectrophotometric assays.

Serum IgA, IgM, IgG, and IgE levels were measured using standard immunoassays, including nephelometry for IgA, IgM, and IgG, and ELISA for IgE (BIOSERV Diagnostics GmbH (Germany)). T-lymphocytes (CD3+, CD19-), T-helpers (CD4+, CD8-), T-cytotoxic cells (CD4-, CD8+), cytotoxic cells (CD3+, CD56+), NK cells (CD3-, CD56+), and B-lymphocytes (CD3-, CD19+) were quantified using flow cytometry. The immunoregulatory index was calculated based on the proportions of T-helpers, T-cytotoxic cells. Monocytes/macrophages (CD14) were also assessed via flow cytometry using CD14-specific antibodies.

2.3. Statistical Analysis

Patient demographics and clinical data were comprehensively analyzed and presented using descriptive statistics. The Shapiro-Wilk test was employed to evaluate the normality of data distribution. Given the non-normal distribution of the data, medians and interquartile ranges were calculated for all variables, and a significance level of $p < 0.05$ was used for hypothesis testing.

Differences between two independent groups were assessed using the Mann-Whitney U test, while the Kruskal-Wallis test was used for comparisons involving three or more groups, with Dunn's multiple comparison test applied for pairwise differences in post hoc analysis.

Spearman's rank correlation coefficient was utilized to explore associations among continuous variables in the correlation matrix analysis.

Binary logistic regression was utilized to identify potential predictors linked to the comorbidity of OA and T2DM. The model quality analysis included the creation of an odds plot and the calculation of ROC metrics, such as the Area Under the ROC Curve (AUC) with a 95% confidence interval (CI), the Youden index (J) with its corresponding cutoff point, as well as sensitivity (Se) and specificity (Sp).

The Wilcoxon signed-rank test was utilized to assess the significance of differences within a group before and after treatment. To compare the differences between groups prior to treatment, the Mann-Whitney U test was employed. The Mann-Whitney U test was also applied to evaluate the differences between groups following treatment.

Statistical analyses were performed using commercially available software packages, including IBM SPSS Statistics (version 25) and GraphPad Prism 10.1.1.

3. Results

3.1. Evaluation of Clinical, Biochemical, and Immunological Parameters in OA and OA+T2DM

Several examined indicators revealed statistically significant differences between the groups (Table 3). The OA+T2DM group presented with elevated levels in WOMAC stiffness, total WOMAC score, Lequesne Algofunctional Index, VAS rest pain, VAS inflammation, VAS joint dysfunction, AIMS-FF, AIMS-SF, and AIMS-GHP ($p < 0.05$). These results indicate that the coexistence of T2DM with OA may intensify symptoms and contribute to more pronounced joint functional impairments.

Table 3. Comparison of OA Indicators Between Patients with OA and OA+T2DM.

	OA (n=52)	OA+T2DM (n=71)	p^a -value
Kellgren-Lawrence grade	2 (2-2)	2 (2-1)	$p^a = 0.469$
WOMAC pain	11 (10-12)	12 (11-13)	$p^a = 0.2091$
WOMAC stiffness	4 (3-5)	5 (4-5)	$p^a = 0.0003$
WOMAC physical function	38 (36-40)	40 (36-44)	$p^a = 0.0529$
Total WOMAC score	54 (51-56)	56 (53.0-60.5)	$p^a = 0.0043$
Lequesne Algofunctional Index	5 (3.75-5)	5 (4-6)	$p^a = 0.0117$
VAS rest pain	32 (26.75-39)	35 (32-39)	$p^a = 0.0371$
VAS movement pain	52 (46-54.25)	51 (48-55)	$p^a = 0.3074$
VAS inflammation	30 (28-32.25)	32 (28.5-36)	$p^a = 0.045$
VAS joint dysfunction	23 (21-25)	24 (22-28)	$p^a = 0.02$
AIMS-FF	2.8 (2.3-3.2)	3 (2.65-3.2)	$p^a = 0.0367$
AIMS-P	2.5 (2.28-2.8)	2.6 (2.2-2.8)	$p^a = 0.9283$
AIMS-SF	1.9 (1.6-2.1)	2 (1.8-2.2)	$p^a = 0.0045$
AIMS-EH	2.15 (1.98-2.3)	2.2 (1.9-2.4)	$p^a = 0.5849$
AIMS-GHP	2.7 (2.4-2.9)	2.9 (2.6-3.2)	$p^a = 0.0035$

Median and interquartile range (IQR) were used to summarize the data. ^a Mann–Whitney test.

A statistically significant elevation was observed in various indicators associated with the progression of type 2 diabetes among patients with comorbid OA and T2DM compared to those in the group with osteoarthritis. Specifically, the OA+T2DM group demonstrated higher levels in fasting blood glucose, C-peptide, HOMA-IR, HbA1c, DDS-17-EB, DDS-17-PRD, DDS-17-RRD, DDS-17-ID, total DDS-17 score, and PAID ($p < 0.001$) (Table 4).

Table 4. Diabetes-Related Metabolic and Psychological Parameter Comparisons Between OA and OA+T2DM Patients.

	OA (n=52)	OA+T2DM (n=71)	p^a -value
Fasting blood glucose, mmol/L	4.2 (4.02-4.38)	6.84 (6.51-7.63)	$p^a < 0.001$
C-peptide, ng/mL	3 (2.51-3.55)	4.54 (3.81-5.14)	$p^a < 0.001$
HOMA-IR	2.68 (2.47-2.83)	3.46 (3.19-3.8)	$p^a < 0.001$
HbA1c, %	5.92 (5.38-6.33)	6.72 (6.55-6.86)	$p^a < 0.001$
DDS-17-EB	1.2 (1.13-1.24)	3.4 (3.15-3.66)	$p^a < 0.001$
DDS-17-PRD	1.1 (1.04-1.17)	4.07 (3.84-4.24)	$p^a < 0.001$
DDS-17-RRD	1.13 (1.07-1.19)	4.29 (4.0-4.5)	$p^a < 0.001$
DDS-17-ID	1.22 (1.13-1.26)	3.99 (3.69-4.35)	$p^a < 0.001$
Total DDS-17 score	1.15 (1.13-1.19)	3.91 (3.77-4.1)	$p^a < 0.001$
PAID	6 (6-6)	34 (31-39)	$p^a < 0.001$

Median and interquartile range (IQR) were used to summarize the data. ^a Mann–Whitney test.

Statistically significant differences were observed in several biomarkers between the OA and OA+T2DM groups. Specifically, the OA+T2DM group had significantly higher levels of neutrophils, NLR, MA, ceruloplasmin, and catalase ($p < 0.05$) (**Table 5**). These findings indicate an exacerbating effect of comorbid type 2 diabetes mellitus on the deterioration of these parameters in osteoarthritis. The increased levels of inflammatory and oxidative stress markers suggest that the presence of T2DM may contribute to a more severe pathological profile and worsening of the clinical status in patients with OA.

Table 5. Comparison of Inflammatory and Biochemical Markers in Patients with OA and OA+T2DM.

	OA (n=52)	OA+T2DM (n=71)	p ^b -value
Leukocytes, 10 ⁹ /L	6.83 (6.19-7.37)	7.07 (6.64-7.57)	$p^a = 0.0664$
Neutrophils, %	53.5 (52-56.25)	56 (52-61)	$p^a = 0.0332$
Lymphocytes, %	21 (19-23.25)	20 (19-22)	$p^a = 0.0343$
NLR	2.55 (2.33-2.7)	2.74 (2.54-3)	$p^a = 0.0003$
CRP, mg/L	4.86 (4.46-5.53)	5.1 (4.83-5.51)	$p^a = 0.0624$
Hydroxyproline, mg/L	1.53 (1.36-1.67)	1.61 (1.35-2.16)	$p^a = 0.066$
MA, μ mol/L.	4.61 (4.02-5.03)	5.04 (4.54-5.42)	$p^a = 0.0008$
Ceruloplasmin, mg/L	388.5 (368.2-408.5)	399 (388.5-410.2)	$p^a = 0.0088$
Kallikrein, μ g/L	153.45 (145-158.4)	156.8 (148.55-162.55)	$p^a = 0.0822$
SOD, U/mL	53.02 (46.81-57.23)	55.3 (50.6-60.7)	$p^a = 0.0711$
Catalase, U/mL	16.74 (15.84-18.24)	18.2 (16.35-20.95)	$p^a = 0.0051$
α_1 -Antitrypsin, g/L:	1.69 (1.63-1.74)	1.7 (1.58-1.81)	$p^a = 0.6375$
α_2 -Macroglobulin, g/L	1.91 (1.86-1.99)	1.89 (1.77-2.05)	$p^a = 0.3204$

Median and interquartile range (IQR) were used to summarize the data. ^a Mann-Whitney test.

In the analysis of immunological parameters, significant differences were detected between the OA and OA+T2DM groups (**Table 6**). Serum IgA and IgE levels were notably higher in the OA+T2DM group ($p < 0.05$). Additionally, the Immunoregulatory Index was significantly elevated in the OA+T2DM group ($p < 0.05$). No significant differences were observed for IgM, IgG, T-Lymphocytes, T-Helpers, T-Cytotoxic Cells, Cytotoxic Cells, NK Cells, B-Lymphocytes, or Monocytes/Macrophages ($p > 0.05$).

Table 6. Comparison of Immunological Markers in Patients with OA and OA+T2DM.

	OA (n=52)	OA+T2DM (n=71)	p ^b -value
Serum IgA, g/L	1.84 (1.73-1.97)	1.93 (1.78-2.11)	$p^a = 0.0218$
IgM, g/L	1.02 (0.9-1.11)	1.05 (0.94-1.21)	$p^a = 0.1328$
IgG, g/L	9.12 (8.49-9.66)	9.08 (8.25-9.68)	$p^a = 0.6616$
IgE, IU/mL	38.8 (37.18-39.59)	40.4 (36.3-45.85)	$p^a = 0.0214$
T-Lymphocytes (CD3+, CD19-), %	59.9 (56.78-62.75)	60.6 (57.5-65.55)	$p^a = 0.0896$
T-Helpers (CD4+, CD8-), %	42.55 (40.35-43.43)	43.5 (40.8-47.4)	$p^a = 0.0795$
T-Cytotoxic Cells (CD4-, CD8+), %	28 (25.48-30.65)	27.7 (26.35-29.75)	$p^a = 0.7645$
Immunoregulatory Index	1.5 (1.4-1.6)	1.6 (1.41-1.72)	$p^a = 0.047$
Cytotoxic Cells (CD3+, CD56+), %	4.7 (4.4-5.03)	4.9 (4.3-5.45)	$p^a = 0.2383$
NK Cells (CD3-, CD56+), %	9.5 (9.2-9.8)	9.7 (8.8-10.65)	$p^a = 0.2447$
B-Lymphocytes (CD3-, CD19+), %	9.75 (9.3-10.3)	10.1 (9.6-10.8)	$p^a = 0.0709$
Monocytes/Macrophages (CD14), %	8.1 (7.9-8.4)	8.2 (7.5-8.85)	$p^a = 0.5743$

Median and interquartile range (IQR) were used to summarize the data. ^a Mann-Whitney test.

3.2. Correlation Analysis of Data in Patients with OA and OA+T2DM

This section explores the correlations among various clinical parameters in OA patients without T2DM. Spearman's rank correlation coefficient (r) was employed to assess the strength and direction of these relationships (Figure 1).

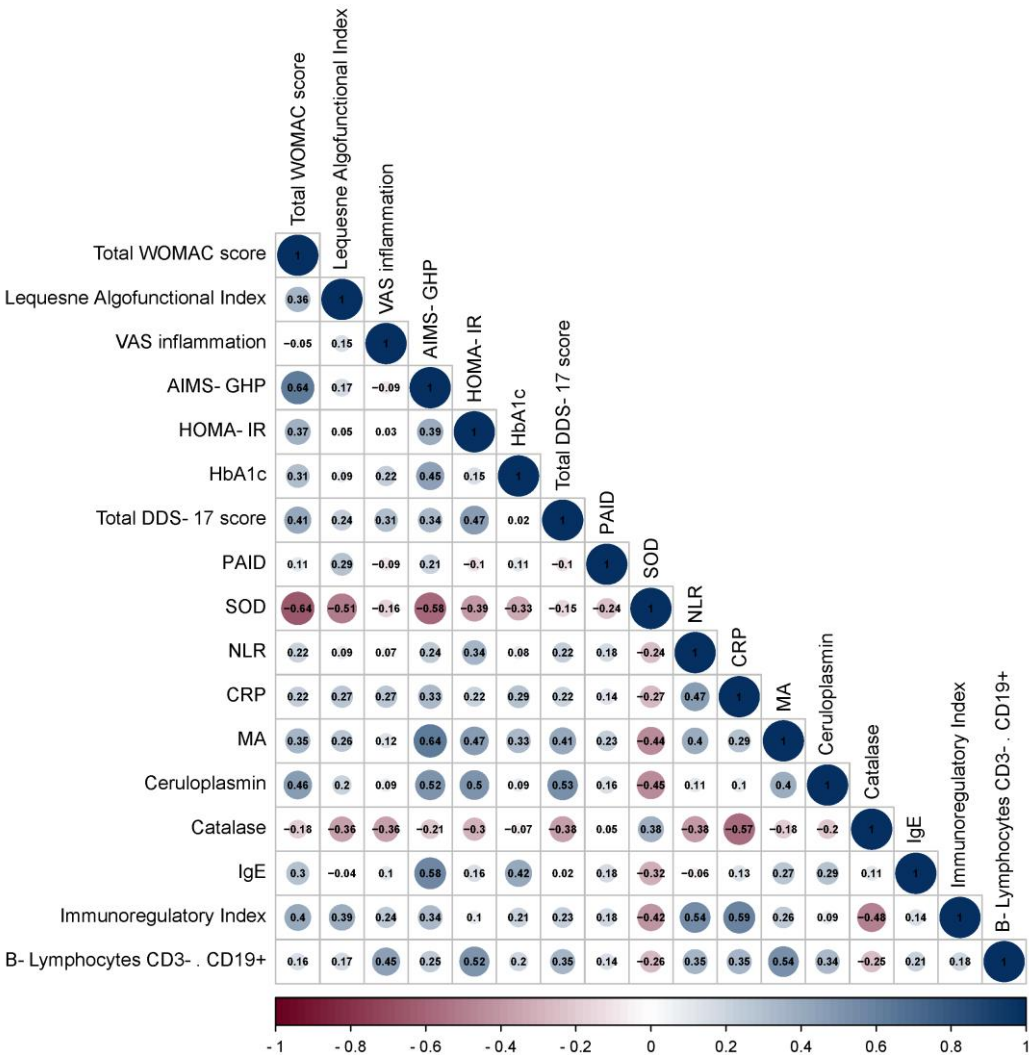


Figure 1. Spearman correlation correlogram used for correlations between data in patients with OA. Red: Strong negative correlation (r = -1.0). Blue: Strong positive correlation (r = 1.0).

The total WOMAC score exhibited positive and negative correlations with several parameters. These correlations included Lequesne Algofunctional Index ($r = 0.36$, $p = 0.009$), AIMS-GHP ($r = 0.64$, $p < 0.001$), HOMA-IR ($r = 0.37$, $p = 0.006$), HbA1c ($r = 0.31$, $p = 0.023$), total DDS-17 score ($r = 0.41$, $p = 0.002$), SOD ($r = -0.64$, $p < 0.001$), MA ($r = 0.35$, $p = 0.011$), ceruloplasmin ($r = 0.46$, $p = 0.001$), IgE ($r = 0.3$, $p = 0.032$), Immunoregulatory Index ($r = 0.4$, $p = 0.003$).

Lequesne Algofunctional Index exhibited positive and negative correlations with PAID ($r = 0.29$, $p = 0.037$), SOD ($r = -0.51$, $p < 0.001$), catalase ($r = -0.36$, $p = 0.009$), Immunoregulatory Index ($r = 0.39$, $p = 0.004$).

VAS inflammation showed positive and negative correlations with total DDS-17 score ($r = 0.31$, $p = 0.027$), catalase ($r = -0.36$, $p = 0.009$), B-Lymphocytes (CD3-. CD19+) ($r = 0.45$, $p < 0.001$).

AIMS-GHP displayed positive and negative correlations with HOMA-IR ($r = 0.39$, $p = 0.004$), HbA1c ($r = 0.45$, $p < 0.001$), total DDS-17 score ($r = 0.34$, $p = 0.015$), SOD ($r = -0.58$, $p < 0.001$), CRP ($r =$

0.33, $p = 0.017$), MA ($r = 0.64$, $p < 0.001$), ceruloplasmin ($r = 0.52$, $p < 0.001$), IgE ($r = 0.58$, $p < 0.001$), Immunoregulatory Index ($r = 0.34$, $p = 0.015$).

HOMA-IR exhibited positive and negative correlations with total DDS-17 score ($r = 0.47$, $p < 0.001$), SOD ($r = -0.39$, $p = 0.005$), NLR ($r = 0.34$, $p = 0.013$), MA ($r = 0.47$, $p < 0.001$), ceruloplasmin ($r = 0.5$, $p < 0.001$), catalase ($r = -0.3$, $p = 0.033$), B-Lymphocytes CD3-. CD19+ ($r = 0.52$, $p < 0.001$).

HbA1c demonstrated positive correlations with SOD ($r = -0.33$, $p = 0.019$), CRP ($r = 0.29$, $p = 0.04$), MA ($r = 0.33$, $p = 0.016$), IgE ($r = 0.42$, $p = 0.002$).

Total DDS-17 score demonstrated positive and negative correlations with MA ($r = 0.41$, $p = 0.002$), ceruloplasmin ($r = 0.53$, $p < 0.001$), catalase ($r = -0.38$, $p = 0.006$), B-Lymphocytes (CD3-. CD19+) ($r = 0.35$, $p = 0.011$).

SOD showed positive and negative correlations with CRP ($r = -0.27$, $p = 0.049$), MA ($r = -0.44$, $p < 0.001$), ceruloplasmin ($r = -0.45$, $p < 0.001$), catalase ($r = 0.38$, $p = 0.006$), IgE ($r = -0.32$, $p = 0.002$), Immunoregulatory Index ($r = -0.42$, $p < 0.001$).

NLR exhibited positive and negative correlations with CRP ($r = 0.47$, $p < 0.001$), MA ($r = 0.4$, $p = 0.004$), catalase ($r = -0.38$, $p = 0.005$), Immunoregulatory Index ($r = 0.54$, $p < 0.001$), B-Lymphocytes (CD3-. CD19+) ($r = 0.35$, $p = 0.012$).

CRP showed positive and negative correlations with MA ($r = 0.4$, $p = 0.034$), catalase ($r = -0.38$, $p < 0.001$), Immunoregulatory Index ($r = 0.59$, $p < 0.001$), B-Lymphocytes (CD3-. CD19+) ($r = 0.35$, $p = 0.011$).

MA demonstrated positive correlations with ceruloplasmin ($r = 0.4$, $p = 0.004$), B-Lymphocytes (CD3-. CD19+) ($r = 0.54$, $p < 0.001$).

Ceruloplasmin exhibited positive correlations with IgE ($r = 0.29$, $p = 0.04$), B-Lymphocytes (CD3-. CD19+) ($r = 0.34$, $p = 0.015$).

Catalase showed a positive correlation with Immunoregulatory Index ($r = -0.48$, $p < 0.001$).

The subsequent section examines the correlations among various clinical parameters in OA patients with T2DM. Spearman's rank correlation coefficient (r) was used to determine the magnitude and direction of these associations (**Figure 2**).

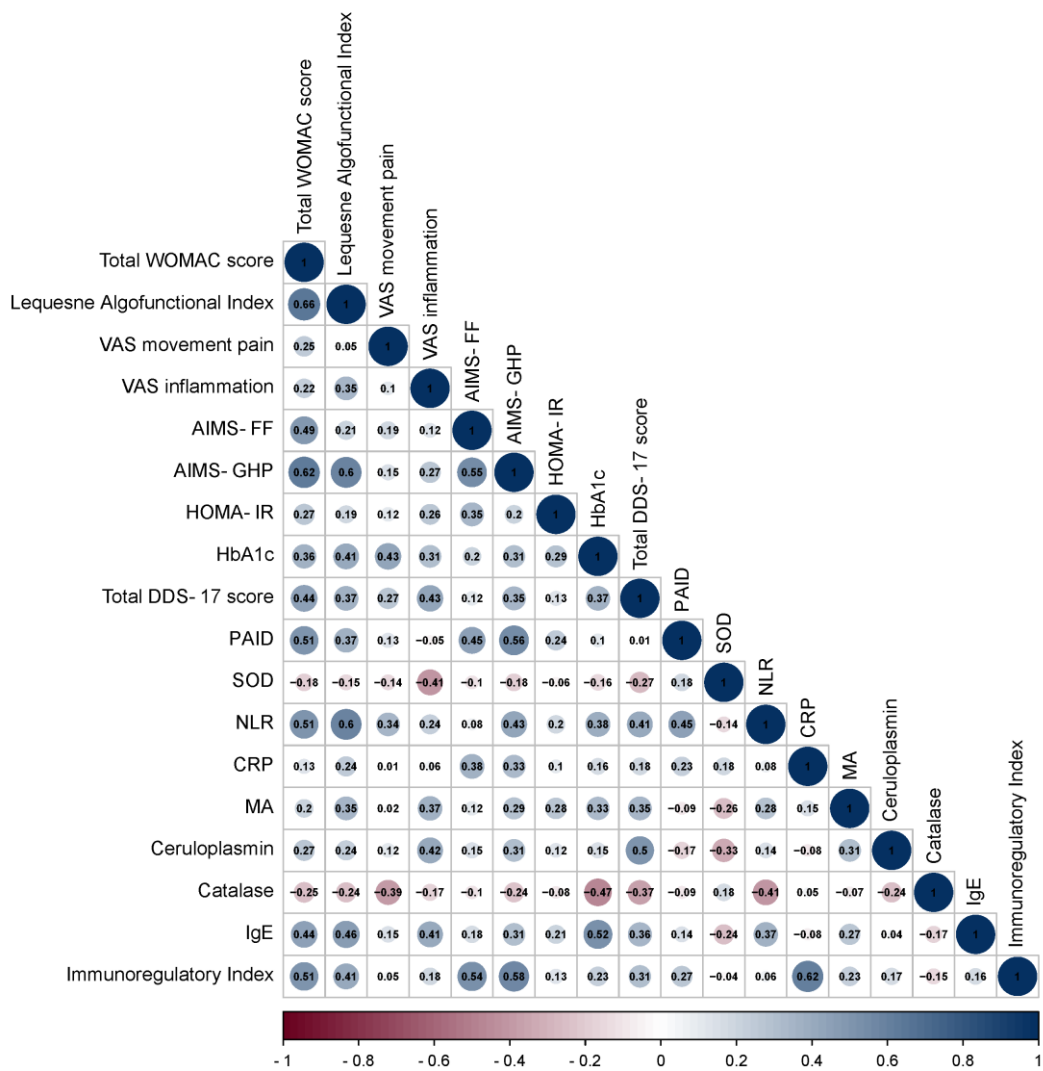


Figure 2. Spearman correlation correlogram used for correlations between data in patients with OA+T2DM. Red: Strong negative correlation ($r = -1.0$). Blue: Strong positive correlation ($r = 1.0$).

Total WOMAC score demonstrated positive and negative correlations with Lequesne Algofunctional Index ($r = 0.66, p < 0.001$), VAS movement pain ($r = 0.25, p = 0.034$), AIMS-FF ($r = 0.49, p < 0.001$), AIMS-GHP ($r = 0.62, p < 0.001$), HOMA-IR ($r = 0.27, p = 0.024$), HbA1c ($r = 0.36, p = 0.002$), total DDS-17 score ($r = 0.44, p < 0.001$), PAID ($r = 0.51, p < 0.001$), NLR ($r = 0.51, p < 0.001$), ceruloplasmin ($r = 0.27, p = 0.024$), catalase ($r = -0.25, p = 0.033$), IgE ($r = 0.44, p < 0.001$), Immunoregulatory Index ($r = 0.51, p < 0.001$).

Lequesne Algofunctional Index showed positive and negative correlations with VAS inflammation ($r = 0.35, p = 0.003$), AIMS-GHP ($r = 0.6, p < 0.001$), HbA1c ($r = 0.41, p < 0.001$), total DDS-17 score ($r = 0.37, p = 0.001$), PAID ($r = 0.37, p = 0.002$), NLR ($r = 0.6, p < 0.001$), CRP ($r = 0.24, p = 0.041$), MA ($r = 0.36, p = 0.003$), ceruloplasmin ($r = 0.24, p = 0.044$), catalase ($r = -0.24, p = 0.043$), IgE ($r = 0.46, p < 0.001$), Immunoregulatory Index ($r = 0.41, p < 0.001$).

VAS movement pain demonstrated positive and negative correlations with HbA1c ($r = 0.43, p < 0.001$), total DDS-17 score ($r = 0.27, p = 0.022$), NLR ($r = 0.34, p = 0.004$), catalase ($r = -0.39, p < 0.001$).

VAS inflammation showed positive and negative correlations with AIMS-GHP ($r = 0.27, p = 0.022$), HOMA-IR ($r = 0.26, p = 0.029$), HbA1c ($r = 0.31, p = 0.008$), total DDS-17 score ($r = 0.43, p < 0.001$), SOD ($r = -0.41, p < 0.001$), NLR ($r = 0.24, p = 0.048$), MA ($r = 0.37, p = 0.002$), ceruloplasmin ($r = 0.42, p < 0.001$), IgE ($r = 0.41, p < 0.001$).

AIMS-FF demonstrated positive correlations with AIMS-GHP ($r = 0.55, p < 0.001$), HOMA-IR ($r = 0.35, p = 0.003$), PAID ($r = 0.45, p < 0.001$), CRP ($r = 0.38, p = 0.001$), Immunoregulatory Index ($r = 0.54, p < 0.001$).

AIMS-GHP showed positive and negative correlations with HbA1c ($r = 0.31, p = 0.009$), total DDS-17 score ($r = 0.35, p = 0.003$), PAID ($r = 0.56, p < 0.001$), NLR ($r = 0.43, p < 0.001$), CRP ($r = 0.33, p = 0.005$), MA ($r = 0.29, p = 0.013$), ceruloplasmin ($r = 0.31, p = 0.008$), catalase ($r = -0.24, p = 0.045$), IgE ($r = 0.31, p = 0.008$), Immunoregulatory Index ($r = 0.58, p < 0.001$).

HOMA-IR exhibited positive correlations with HbA1c ($r = 0.29, p = 0.013$), PAID ($r = 0.24, p = 0.041$), MA ($r = 0.28, p = 0.019$).

HbA1c demonstrated positive and negative correlations with total DDS-17 score ($r = 0.37, p = 0.002$), NLR ($r = 0.38, p < 0.001$), MA ($r = 0.33, p = 0.005$), catalase ($r = -0.47, p < 0.001$), IgE ($r = 0.52, p < 0.001$).

Total DDS-17 score showed positive and negative correlations with SOD ($r = -0.27, p = 0.024$), NLR ($r = 0.41, p < 0.001$), MA ($r = 0.35, p = 0.003$), ceruloplasmin ($r = 0.5, p < 0.001$), catalase ($r = -0.37, p = 0.002$), IgE ($r = 0.36, p = 0.002$), Immunoregulatory Index ($r = 0.31, p = 0.01$).

PAID demonstrated positive correlations with NLR ($r = 0.45, p < 0.001$), Immunoregulatory Index ($r = 0.27, p = 0.025$).

SOD exhibited positive correlations with MA ($r = -0.26, p = 0.029$), ceruloplasmin ($r = -0.33, p = 0.005$), IgE ($r = -0.24, p = 0.041$).

NLR demonstrated positive and negative correlations with MA ($r = 0.28, p = 0.017$), catalase ($r = -0.41, p < 0.001$), IgE ($r = 0.37, p = 0.001$).

CRP exhibited a positive correlation with Immunoregulatory Index ($r = 0.62, p < 0.001$).

MA showed positive correlations with ceruloplasmin ($r = 0.31, p = 0.008$), IgE ($r = 0.27, p = 0.022$).

Ceruloplasmin demonstrated a negative correlation with catalase ($r = -0.24, p = 0.04$).

3.3. Binary Logistic Regression of Data in Patients with OA and OA+T2DM

A prognostic model for predicting a binary outcome was developed using logistic regression, with model performance assessed by Nagelkerke R^2 .

ROC analysis was employed to evaluate the diagnostic efficacy of quantitative variables in predicting a categorical outcome. The optimal cut-off value for the quantitative variable was determined using Youden's J statistic. Statistical significance was defined as $p < 0.05$.

A predictive model was constructed to estimate the probability of group membership based on HOMA-IR, HbA1c, and serum IgA using binary logistic regression. The analysis included 123 observations. The observed relationship is represented by the following equation: $P = 1 / (1 + e^{-z}) \times 100\%$

$$z = -52.027 + 8.517X_{\text{HOMA-IR}} + 1.812X_{\text{HbA1c}} + 7.744X_{\text{Serum IgA}}$$

where p – probability of OA+T2DM, $X_{\text{HOMA-IR}}$ – HOMA-IR, X_{HbA1c} – HbA1c, $X_{\text{Serum IgA}}$ – Serum IgA

The regression model produced is statistically significant ($p < 0.001$). According to Nagelkerke R^2 , the model accounts for 86.0% of the variance in the observed group. An increase of one unit in HOMA-IR is associated with a 4997.535-fold increase in the odds of OA+T2DM. Similarly, a one-unit increase in HbA1c is linked to a 6.120-fold increase in the odds of OA+T2DM, while a one-unit increase in serum IgA is associated with a 2306.762-fold increase in these odds (Table 7) (Figure 3).

Table 7. Characteristics of the association of predictors with the probability of Group.

Predictors	Unadjusted		Adjusted	
	COR; 95% CI	<i>p</i>	AOR; 95% CI	<i>p</i>
HOMA-IR	2065.650; 121.146 – 35206.993	< 0.001*	4997.535; 116.980 – 213416.301	< 0.001*
HbA1c	14.986; 5.387 – 41.679	< 0.001*	6.120; 1.239 – 30.235	0.026*

Serum IgA	9.210; 1.459 – 58.090	0.018*	2306.762; 14.182 – 375119.530	0.003*
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* – association of the outcome value with the predictor value is statistically significant (p < 0.05).

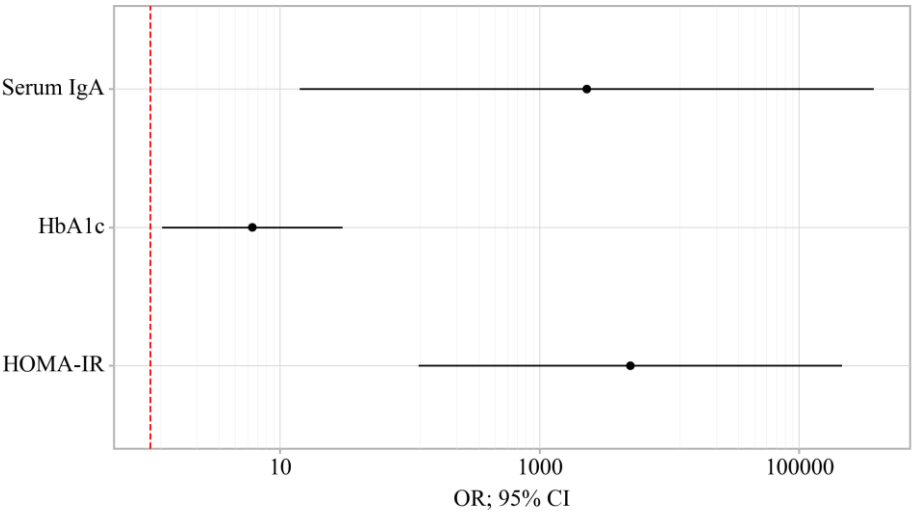


Figure 3. Odds ratios estimates with corresponding 95% CI's for predictors included to the model Group.

When assessing the dependence of the probability of OA+T2DM on the logistic function value P through ROC analysis, the resulting curve was obtained (**Figure 4**).

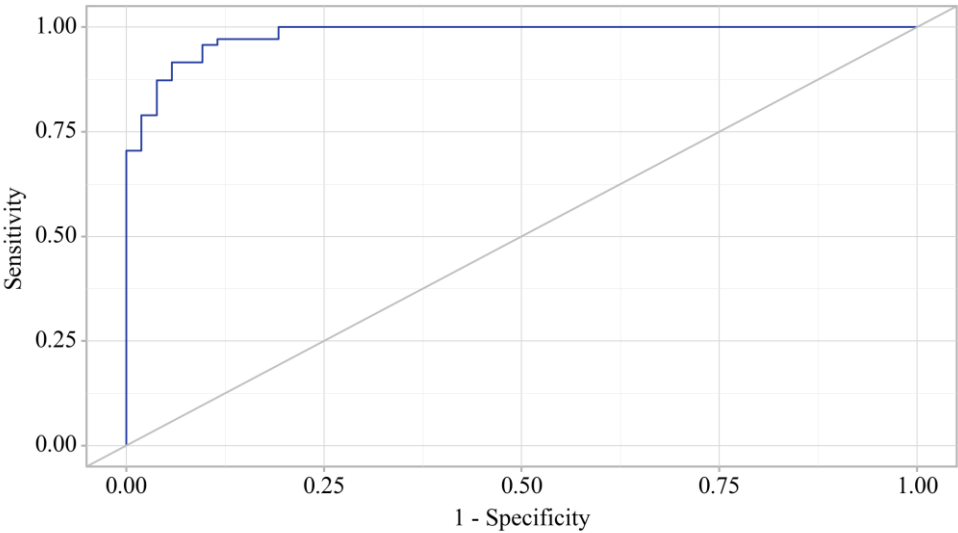


Figure 4. ROC-curve characterizing the dependence of the probability Group on Value of logistic function P.

The area under the ROC curve was 0.982 ± 0.012 , with a 95% confidence interval of 0.959 to 1.000, indicating statistical significance ($p < 0.001$). The cut-off value for the logistic function P that yielded the highest Youden's J statistic was 0.530 (**Figure 5**).

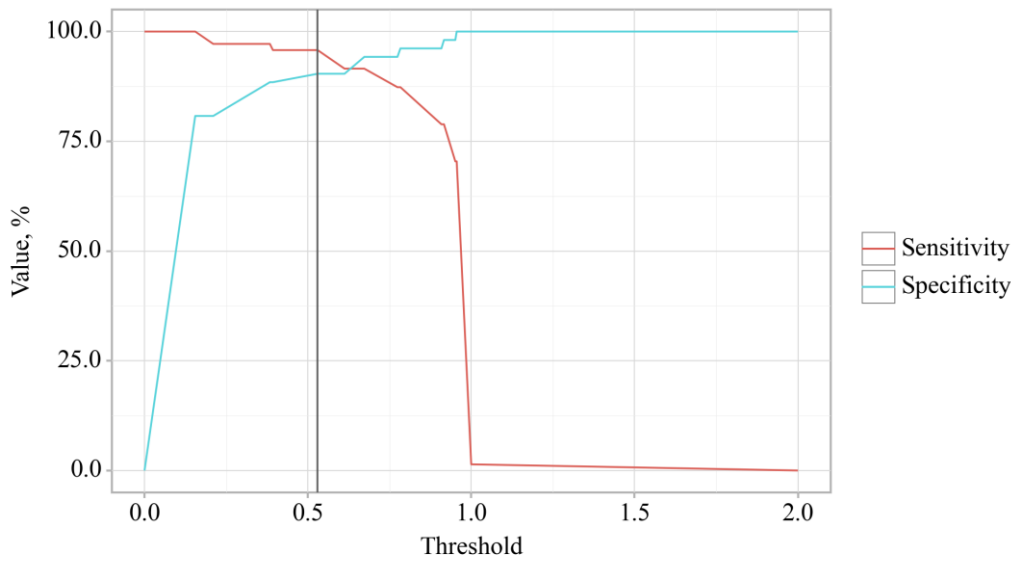


Figure 5. Analysis of the sensitivity and specificity of Group depending on Value of logistic function P.

A logistic function P value equal to or greater than this threshold predicted OA+T2DM. The method demonstrated a sensitivity of 95.8% and a specificity of 90.4%.

3.4. Comparative Analysis of Treatment Outcomes in Patients with OA and T2DM With and Without ALA Supplementation

The statistical evaluation of the parameters before and after treatment revealed significant changes (Table 8). In the group without ALA, notable improvements were observed in WOMAC pain, WOMAC stiffness, WOMAC physical function, Total WOMAC score, Lequesne Algofunctional Index, VAS rest pain, VAS movement pain, VAS inflammation, VAS joint dysfunction, AIMS-FF and AIMS-SF ($p < 0.05$). Conversely, the group with ALA exhibited significant enhancements in WOMAC pain, WOMAC physical function, Total WOMAC score, Lequesne Algofunctional Index, VAS rest pain, VAS movement pain, VAS inflammation, VAS joint dysfunction, AIMS-FF, AIMS-P, AIMS-SF, AIMS-EH, AIMS-GHP ($p < 0.05$). Comparative analysis between the groups after treatment highlighted that the effects of treatment were more pronounced in the ALA group, particularly for WOMAC pain, Lequesne Algofunctional Index, VAS joint dysfunction, AIMS-FF, AIMS-EH ($p < 0.05$) (Figure 6).

Table 8. Comparison of Osteoarthritis Indicators Before and After Treatment in Groups with and without ALA.

	Group without ALA (n=37)		Group with ALA (n=34)		<i>p</i> ^{bc} -value
	Before treatment	After treatment	Before treatment	After treatment	
Kellgren-Lawrence grade	2 (1-2)	2 (1-2)	2 (1.25-2)	2 (1-2)	<i>p</i> ^b = 0.7395
<i>p</i>^a-value		<i>p</i> ^a = 0.233		<i>p</i> ^a = 0.484	<i>p</i> ^c = 0.7298
WOMAC pain	11 (10-13)	11 (9-12)	12 (11-13)	9 (8-11)	<i>p</i> ^b = 0.4518
<i>p</i>^a-value		<i>p</i> ^a = 0.0321		<i>p</i> ^a = 0.0014	<i>p</i> ^c = 0.0390
WOMAC stiffness	5 (4-6)	4 (4-5)	5 (4-5)	4 (3-4)	<i>p</i> ^b = 0.1993
<i>p</i>^a-value		<i>p</i> ^a = 0.0010		<i>p</i> ^a = 0.0055	<i>p</i> ^c = 0.1937
WOMAC physical function	40 (35-44)	37 (35-39)	40 (36.25-43.75)	36.5 (35-38.75)	<i>p</i> ^b = 0.7996
<i>p</i>^a-value		<i>p</i> ^a = 0.055		<i>p</i> ^a = 0.0049	<i>p</i> ^c = 0.9538

Total WOMAC score	56 (53-61)	52 (48-53)	56.5 (53.25-59.75)	50 (47-53)	$p^b = 0.8853$
p^{ac} -value	$p^a = 0.0028$		$p^a = < 0.001$		$p^c = 0.1876$
Lequesne	5 (4-6)	4 (3-5)	5 (4-5.75)	3 (2-4)	$p^b = 0.5299$
Algofunctional Index					
p^{ac} -value	$p^a = 0.0006$		$p^a = < 0.001$		$p^c = 0.0172$
VAS rest pain	37 (32-40)	30 (27-34)	34 (32-38)	30.5 (28-34)	$p^b = 0.1541$
p^{ac} -value	$p^a < 0.001$		$p^a < 0.001$		$p^c = 0.751$
VAS movement pain	52 (48-54)	50 (43-53)	50.5 (46.25-58.5)	46.5 (39.5-50.75)	$p^b = 0.624$
p^{ac} -value	$p^a = 0.0461$		$p^a = 0.0049$		$p^c = 0.0619$
VAS inflammation	32 (28-34)	27 (22-31)	33 (29.25-37)	26 (24-28.75)	$p^b = 0.3127$
p^{ac} -value	$p^a = 0.0113$		$p^a < 0.001$		$p^c = 0.5757$
VAS joint dysfunction	24 (22-28)	21 (19-24)	24.5 (21.25-28.75)	19 (17-22)	$p^b = 0.9586$
p^{ac} -value	$p^a = 0.0089$		$p^a = 0.0004$		$p^c = 0.0497$
AIMS-FF	3.1 (2.7-3.2)	2.7 (2.5-3)	2.9 (2.6-3.18)	2.5 (2.23-2.8)	$p^b = 0.3611$
p^{ac} -value	$p^a = 0.0121$		$p^a = 0.0026$		$p^c = 0.0142$
AIMS-P	2.5 (2.2-2.8)	2.3 (2-2.6)	2.6 (2.4-2.78)	2 (1.8-2.3)	$p^b = 0.4018$
p^{ac} -value	$p^a = 0.3564$		$p^a < 0.001$		$p^c = 0.0073$
AIMS-SF	2 (1.9-2.2)	1.9 (1.7-2)	2 (1.73-2.2)	1.75 (1.6-1.9)	$p^b = 0.3663$
p^{ac} -value	$p^a = 0.0241$		$p^a = 0.0146$		$p^c = 0.1003$
AIMS-EH	2.2 (2-2.3)	2.1 (1.9-2.2)	2.1 (1.9-2.4)	2 (1.7-2.1)	$p^b = 0.5388$
p^{ac} -value	$p^a = 0.2196$		$p^a = 0.0055$		$p^c = 0.0083$
AIMS-GHP	2.9 (2.6-3.1)	2.7 (2.4-3)	2.9 (2.7-3.28)	2.6 (2.43-2.7)	$p^b = 0.3616$
p^{ac} -value	$p^a = 0.0907$		$p^a = 0.0004$		$p^c = 0.2377$

Median and interquartile range (IQR) were used to summarize the data. ^a the statistical difference observed within the group before and after treatment, based on the Wilcoxon signed-rank test. ^b the statistical difference between groups before treatment, based on the Mann-Whitney U test. ^c the statistical difference between groups after treatment, based on the Mann-Whitney U test.

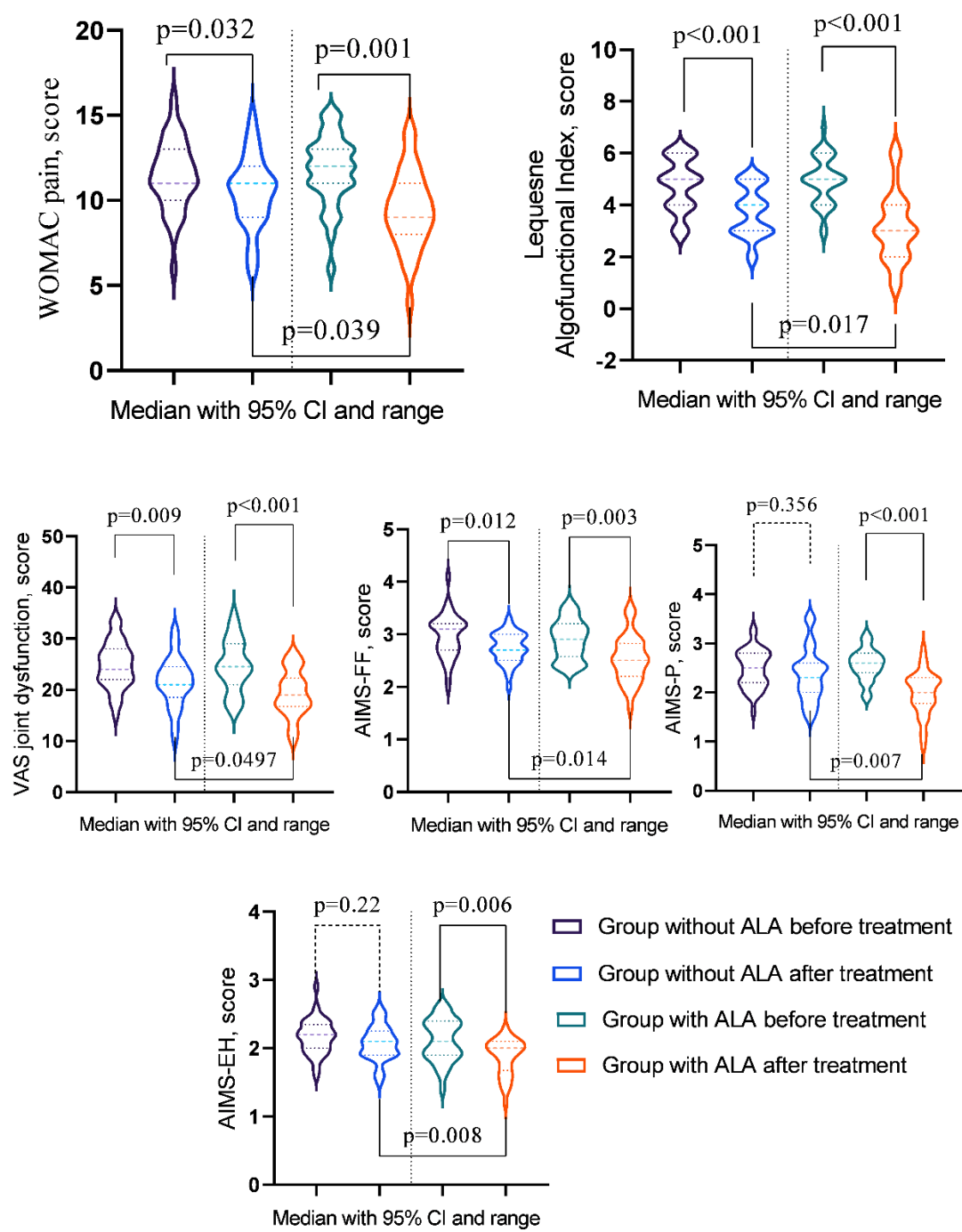


Figure 6. Osteoarthritis Indicators Showing Significant Changes Post-Treatment Across Groups.

In the analysis of T2DM progression indicators before and after treatment (**Table 9**), significant improvements were observed across several parameters. In the group not receiving ALA, notable reductions were seen in fasting blood glucose levels, DDS-17-EB, DDS-17-RRD, and PAID ($p < 0.05$). In contrast, the group treated with ALA demonstrated significant improvements in fasting blood glucose levels, DDS-17-EB, DDS-17-RRD, DDS-17-ID, and PAID ($p < 0.05$). Post-treatment comparisons between the groups revealed that the ALA group experienced more substantial benefits, particularly in DDS-17-EB and PAID ($p < 0.05$) (**Figure 7**).

Table 9. Comparison of Diabetes Indicators Before and After Treatment in Groups with and without ALA.

		Group without ALA (n=37)		Group with ALA (n=34)		p ^{bc} -value
		Before treatment	After treatment	Before treatment	After treatment	
Fasting blood glucose, mmol/L		6.87 (6.5-7.24)	6.52 (6.17-6.8)	6.8 (6.54-7.79)	6.47 (5.8-6.99)	p ^b = 0,427
p ^{ac} -value		p ^a = 0,0271		p ^a = 0,003		p ^c = 0.881
C-peptide, ng/mL		4.49 (3.88-4.96)	4.23 (3.78-4.92)	4.55 (3.56-5.58)	4.22 (3.88-4.79)	p ^b = 0,8674
p ^{ac} -value		p ^a = 0,4689		p ^a = 0,1768		p ^c = 0,8539
HOMA-IR		3.49 (3.19-3.75)	3.4 (3.18-3.6)	3.45 (3.2-3.83)	3.35 (2.87-3.69)	p ^b = 0.8992
p ^{ac} -value		p ^a = 0,261		p ^a = 0,093		p ^c = 0,6452
HbA1c, %		6.7 (6.38-7.25)	6.49 (6.34-6.96)	6.73 (6.63-6.79)	6.63 (6.41-6.94)	p ^b = 0.9449
p ^{ac} -value		p ^a = 0.2642		p ^a = 0.3308		p ^c = 0.5805
DDS-17-EB		3.4 (3.05-3.66)	3.2 (3.11-3.29)	3.4 (3.18-3.65)	3.1 (2.94-3.19)	p ^b = 0.9266
p ^{ac} -value		p ^a = 0.0022		p ^a = 0.0001		p ^c = 0.0035
DDS-17-PRD		4.07 (3.82-4.23)	3.89 (3.51-4.11)	4.11 (3.92-4.25)	3.73 (3.42-4.02)	p ^b = 0.4439
p ^{ac} -value		p ^a = 0.1843		p ^a = 0.0022		p ^c = 0.4406
DDS-17-RRD		4.3 (4.03-4.53)	3.88 (3.69-4.18)	4.25 (3.99-4.47)	3.85 (3.72-3.98)	p ^b = 0.7385
p ^{ac} -value		p ^a = 0.0036		p ^a < 0.001		p ^c = 0.4718
DDS-17-ID		3.93 (3.57-4.29)	3.86 (3.41-4.2)	4.02 (3.75-4.41)	3.66 (3.3-3.96)	p ^b = 0.4007
p ^{ac} -value		p ^a = 0.3898		p ^a = 0.0183		p ^c = 0.4405
Total DDS-17 score		3.88 (3.76-4.1)	3.71 (3.57-3.78)	3.97 (3.77-4.09)	3.55 (3.45-3.72)	p ^b = 0.9634
p ^{ac} -value		p ^a = 0.6635		p ^a = 0.7301		p ^c = 0.7596
PAID		35 (32-39)	31 (28-34)	33.5 (30.25-37.75)	29.5 (26.25-31.75)	p ^b = 0.3837
p ^{ac} -value		p ^a = 0.0012		p ^a = 0.0002		p ^c = 0.0293

Median and interquartile range (IQR) were used to summarize the data. ^a the statistical difference observed within the group before and after treatment, based on the Wilcoxon signed-rank test. ^b the statistical difference between groups before treatment, based on the Mann-Whitney U test. ^c the statistical difference between groups after treatment, based on the Mann-Whitney U test.

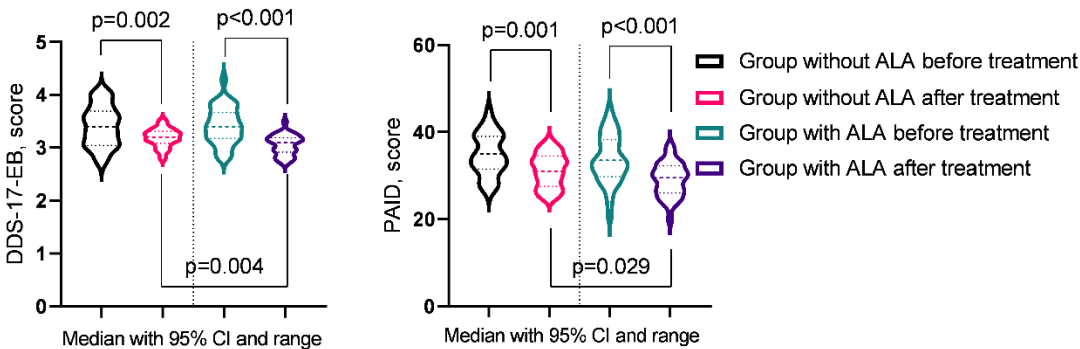


Figure 7. Diabetes Indicators Showing Significant Changes Post-Treatment Across Groups.

The analysis of outcomes before and after treatment revealed significant differences in inflammatory markers, oxidative stress parameters, and leukocyte subpopulations between the groups (Table 10). In the group not receiving ALA, statistically significant changes were observed in NLR, CRP, and catalase levels ($p < 0.05$). Conversely, in the group treated with ALA, significant alterations were noted in leukocyte counts, neutrophil percentages, NLR, CRP, MA, ceruloplasmin, SOD, and catalase ($p < 0.05$). Additionally, biomarkers after treatment comparisons between the groups highlighted a statistically significant difference in CRP levels ($p < 0.05$) (Figure 8).

Table 10. Comparison of Biomarkers Before and After Treatment in Groups with and without ALA.

	Group without ALA (n=37)		Group with ALA (n=34)		p ^{bc} -value
	Before treatment	After treatment	Before treatment	After treatment	
Leukocytes, 10 ⁹ /L	7.26 (6.64-7.63)	7.04 (6.19-7.43)	7.02 (6.63-7.29)	6.55 (6.06-6.87)	p ^b = 0.2224
p ^{ac} -value	p ^a = 0.1534		p ^a = 0.0024		p ^c = 0.0622
Neutrophils, %	56 (50-59)	54 (50-56)	57 (53-61,75)	55 (50.25-61.75)	p ^b = 0.0889
p ^{ac} -value	p ^a = 0.1366		p ^a = 0.0054		p ^c = 0.2517
Lymphocytes, %	19 (19-21)	21 (19-22)	20 (19-23.75)	22 (20-24)	p ^b = 0.1237
p ^{ac} -value	p ^a = 0.3266		p ^a = 0.1269		p ^c = 0.0078
NLR	2.74 (2.55-2.94)	2.52 (2.39-2.78)	2.76 (2.54-3.08)	2.42 (2.25-2.68)	p ^b = 0.4789
p ^{ac} -value	p ^a = 0.0132		p ^a = 0.0023		p ^c = 0.0893
CRP, mg/L	5.16 (4.95-5.48)	4.85 (4.38-5.2)	5.02 (4.63-5.54)	4.58 (4.11-5.16)	p ^b = 0,1286
p ^{ac} -value	p ^a = 0.001		p ^a = 0.0078		p ^c = 0,0119
Hydroxyproline, mg/L	1.61 (1.22-1.87)	1.64 (1.32-1.8)	1.64 (1.38-2.27)	1.47 (1.12-2.04)	p ^b = 0.497
p ^{ac} -value	p ^a = 0.7571		p ^a = 0.1324		p ^c = 0.7472
MA, μmol/L.	5.04 (4.69-5.39)	4.81 (4.32-5.42)	5.04 (4.44-5.6)	4.44 (3.93-5.05)	p ^b = 0.8449
p ^{ac} -value	p ^a = 0.1056		p ^a = 0.0031		p ^c = 0.0546
Ceruloplasmin, mg/L	397.5 (387.1-410.5)	390.2 (383.5-409.3)	405 (391-408.4)	388.1 (372.3-397.6)	p ^b = 0.5118
p ^{ac} -value	p ^a = 0.1491		p ^a = 0.0019		p ^c = 0.1272
Kallikrein, μg/L	153.7 (148.2-162.4)	152.1 (146.7-156.9)	157.5 (150.4-162.5)	152.2 (145-159.5)	p ^b = 0.5885
p ^{ac} -value	p ^a = 0.2364		p ^a = 0.1043		p ^c = 0.7912
SOD, U/mL	57.5 (52.2-61.5)	59.3 (55.5-63.3)	54.75 (47.83-59.68)	58.3 (53.7-63.58)	p ^b = 0.1837
p ^{ac} -value	p ^a = 0.2189		p ^a = 0.0033		p ^c = 0.5229
Catalase, U/mL	18.3 (16.8-20.1)	20.5 (18.43-23.26)	17.7 (15.23-21.73)	21.95 (20.45-23.98)	p ^b = 0.8314
p ^{ac} -value	p ^a = 0.0146		p ^a = 0.0014		p ^c = 0.1258
α ₁ -Antitrypsin, g/L	1.7 (1.57-1.78)	1.7 (1.51-1.76)	1.71 (1.59-1.83)	1.61 (1.45-1.79)	p ^b = 0.6083
p ^{ac} -value	p ^a = 0.7571		p ^a = 0.1744		p ^c = 0.4303
α ₂ -Macroglobulin, g/L	1.88 (1.78-1.99)	1.99 (1.79-2.09)	1.9 (1.7-2.11)	1.93 (1.84-2.12)	p ^b = 0.7956
p ^{ac} -value	p ^a = 0.245		p ^a = 0.0889		p ^c = 0.6827

Median and interquartile range (IQR) were used to summarize the data. ^a the statistical difference observed within the group before and after treatment, based on the Wilcoxon signed-rank test. ^b the statistical difference between groups before treatment, based on the Mann-Whitney U test. ^c the statistical difference between groups after treatment, based on the Mann-Whitney U test.

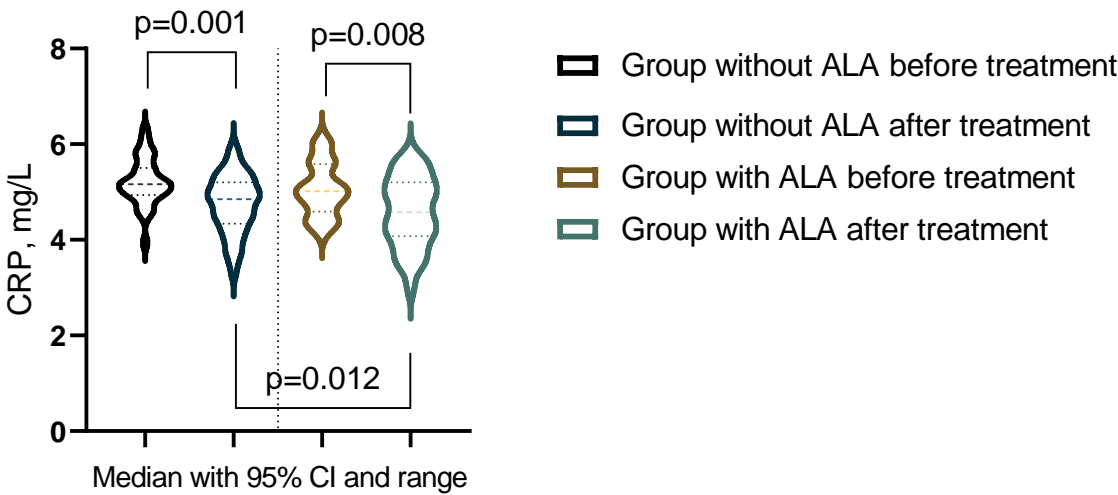


Figure 8. Biomarker Showing Significant Changes Post-Treatment Across Groups.

The analysis indicated differential responses in immunological markers to treatment across the study groups (Table 11). In the group that did not receive ALA, no statistically significant changes were observed in the immunological markers ($p > 0.05$). In contrast, the group treated with ALA showed significant post-treatment changes in serum IgA, IgE, and the Immunoregulatory Index ($p < 0.05$). Moreover, a significant difference in IgE levels was observed when comparing post-treatment levels between the groups across the studied markers ($p < 0.05$) (Figure 9).

Table 11. Comparison of Immunological Markers Before and After Treatment in Groups with and without ALA.

	Group without ALA (n=37)		Group with ALA (n=34)		p ^{bc} -value
	Before treatment	After treatment	Before treatment	After treatment	
Serum IgA, g/L	1.93 (1.79-2.11)	1.87 (1.69-2.08)	1.92 (1.76-2.09)	1.84 (1.56-2.04)	p ^b =0.9175
p ^{ac} -value	p ^a =0.02204		p ^a = 0.0251		p ^c = 0.3422
IgM, g/L	1.08 (1.02-1.21)	0.99 (0.84-1.19)	0.99 (0.89-1.2)	0.99 (0.71-1.13)	p ^b = 0.0811
p ^{ac} -value	p ^a = 0.2133		p ^a = 0.1438		p ^c = 0.4071
IgG, g/L	8.74 (8.26-9.41)	8.81 (8.23-9.76)	9.22 (8.19-9.74)	8.59 (8.17-9.45)	p ^b = 0.4204
p ^{ac} -value	p ^a = 0.7399		p ^a = 0.3303		p ^c = 0.6786
IgE, IU/mL	40.4 (35.4-47.6)	39.7 (34.6-43.9)	40.6 (36.93-44.15)	35.15 (32.75-38.08)	p ^b = 0.704
p ^{ac} -value	p ^a = 0.4275		p ^a = 0.0008		p ^c = 0.0244
T-Lymphocytes (CD3+, CD19-), %	61 (56.6-65.4)	57.2 (53.8-64.9)	60 (57.58-66.03)	58.6 (53.13-63.18)	p ^b = 0.7255
p ^{ac} -value	p ^a = 0.1017		p ^a = 0.099		p ^c = 0.8001
T-Helpers (CD4+, CD8-), %	43.5 (41-46.9)	42.6 (40.1-44.9)	44.95 (40.28-47.85)	40.45 (38.7-44.98)	p ^b = 0.872
p ^{ac} -value	p ^a = 0.4736		p ^a = 0.0566		p ^c = 0.2617
T-Cytotoxic Cells (CD4-, CD8+), %	28.2 (26.4-29.8)	29.5 (26-30.8)	27.45 (26.08-29.5)	28.45 (27.1-32.25)	p ^b = 0.508
p ^{ac} -value	p ^a = 0.6838		p ^a = 0.513		p ^c = 0.2766
Immunoregulatory Index	1.61 (1.39-1.64)	1.47 (1.4-1.67)	1.59 (1.42-1.76)	1.4 (1.27-1.55)	p ^b = 0.6247
p ^{ac} -value	p ^a = 0.2677		p ^a = 0.0125		p ^c = 0.056
Cytotoxic Cells (CD3+, CD56+), %	4.8 (4.3-5.5)	4.8 (4.4-5.2)	4.9 (4.33-5.4)	4.85 (4.3-5.1)	p ^b = 0.7294
p ^{ac} -value	p ^a = 0.5724		p ^a = 0.6939		p ^c = 0.7251

NK Cells (CD3-, CD56+), %	10.3 (9-10.8)	9.5 (8.7-10.7)	9.4 (8.73-10.55)	9.15 (8.5-9.78)	p ^b = 0.2332
p ^{ac} -value	p ^a = 0.1996		p ^a = 0.3879		p ^c = 0.1389
B-Lymphocytes (CD3-, CD19+), %	10 (9.7-10.5)	9.9 (9.3-10.7)	10.2 (9.45-10.9)	9.65 (8.03-10.45)	p ^b = 0.7427
p ^{ac} -value	p ^a = 0.8741		p ^a = 0.0887		p ^c = 0.1499
Monocytes/Macrophages (CD14), %	8.2 (7.5-9)	8.1 (7.2-8.7)	8.15 (7.55-8.58)	7.65 (7.13-8.48)	p ^b = 0.5684
p ^{ac} -value	p ^a = 0.2233		p ^a = 0.2814		p ^c = 0.4403

Median and interquartile range (IQR) were used to summarize the data. ^a the statistical difference observed within the group before and after treatment, based on the Wilcoxon signed-rank test. ^b the statistical difference between groups before treatment, based on the Mann-Whitney U test. ^c the statistical difference between groups after treatment, based on the Mann-Whitney U test.

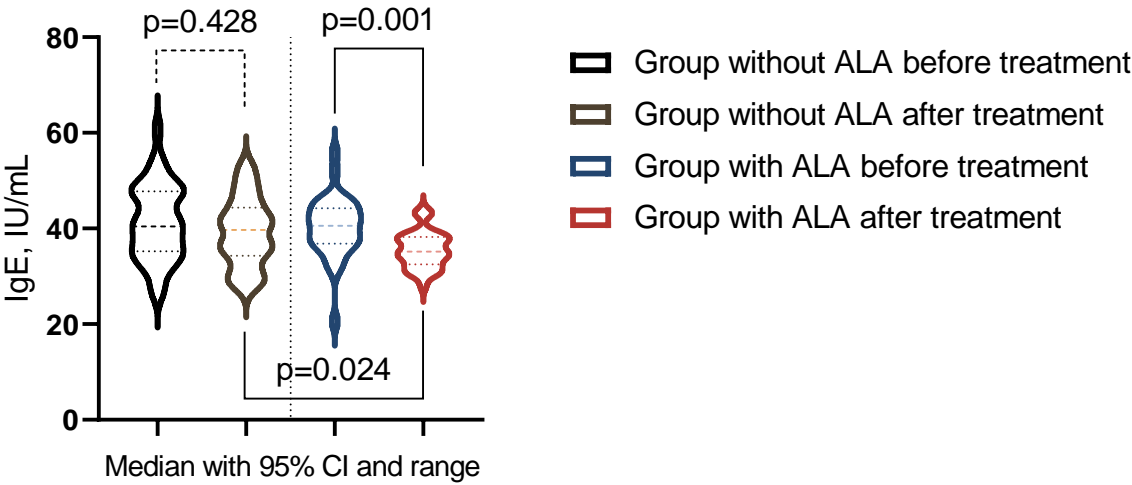


Figure 9. Immunological Indicator Showing Significant Changes Post-Treatment Across Groups.

4. Discussion

This study sheds light on the intricate relationship between T2DM and OA, demonstrating how the coexistence of these conditions significantly exacerbates clinical symptoms and biochemical markers in affected patients. These findings are consistent with previous studies that have reported similar associations between T2DM and the worsening of OA [29–32]. For instance, prior research has shown that patients with both T2DM and OA often experience more severe pain and greater functional limitations compared to those with OA alone [14,33–36]. This study aligns with these observations, further supporting the notion that T2DM acts as an aggravating factor in OA progression.

The increased levels of inflammation, oxidative stress, and immune disturbances observed in this study's cohort mirror findings from other research [10,37–38]. Elevated CRP levels, a marker of systemic inflammation, have been consistently reported in patients with T2DM [39–40], and their further elevation in the context of OA suggests a synergistic effect of these conditions on inflammatory processes [30,41]. Previous studies have also highlighted the role of oxidative stress in comorbid T2DM and OA [38,42], with some research indicating that oxidative damage may contribute to cartilage degradation and joint dysfunction [43–45]. The current study's findings reinforce these insights, showing that oxidative stress is markedly higher in patients with comorbid T2DM and OA, thereby linking metabolic disturbances with joint pathology.

Moreover, this study's identification of significant correlations among metabolic, psychological, and inflammatory factors in patients with both T2DM and OA adds a new dimension to our understanding of this comorbidity. While earlier research has explored the individual impact of these

factors [34,46–49], the present study underscores their interconnectedness, suggesting that managing one aspect of this triad may influence the others. For example, addressing metabolic dysregulation in T2DM could potentially reduce inflammation and improve psychological well-being, which in turn might slow the progression of OA [50–52]. This holistic view aligns with recent studies advocating for integrated treatment approaches that consider the multifactorial nature of comorbid conditions [53–55]. T2DM is managed by targeting metabolic alterations, with metformin being a key pharmacological agent [56–58]. It effectively improves insulin sensitivity, decreases hepatic glucose production, and enhances peripheral glucose uptake, thereby aiding in the normalization of metabolic parameters in individuals with T2DM [59–63].

The study's exploration of ALA as a therapeutic adjunct also contributes to the growing body of evidence supporting its use in metabolic disorders. Previous studies have demonstrated ALA's effectiveness in improving insulin sensitivity and reducing oxidative stress (**Figure 10**) [64–66]. Recent research indicates that the administration of alpha-lipoic acid is associated with a significant reduction in systemic inflammation. This effect highlights its potential as a therapeutic agent in the management of inflammatory processes in various conditions (**Figure 11**) [67–70].

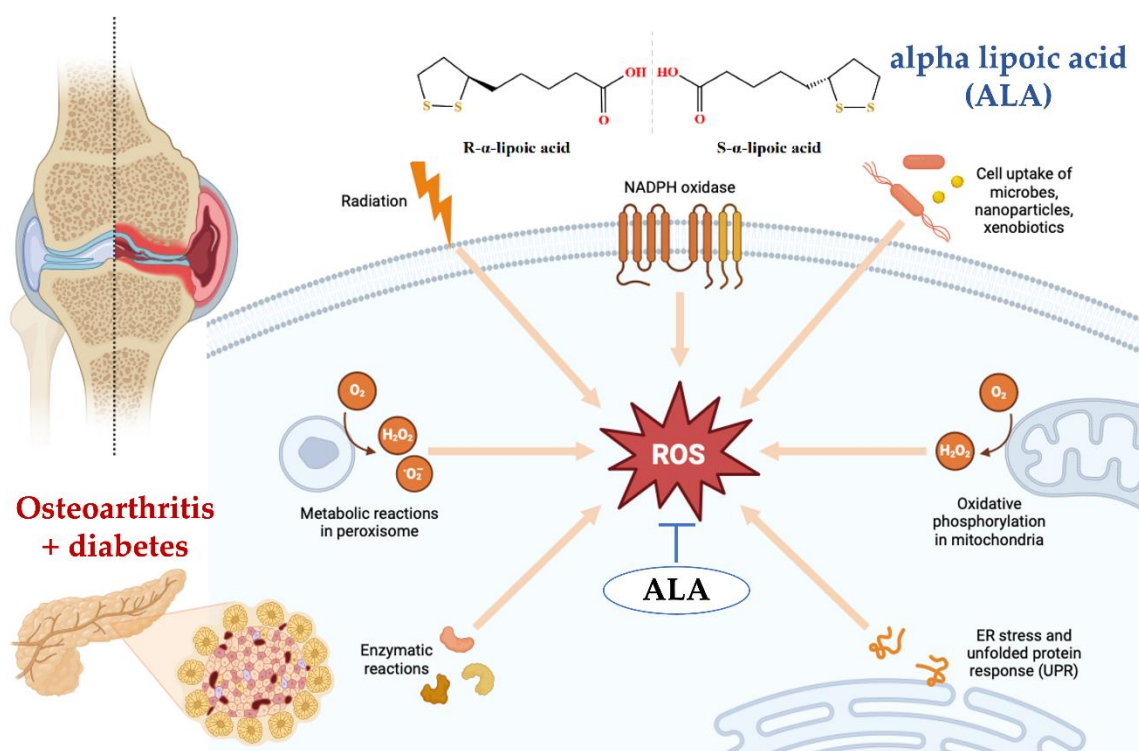


Figure 10. Alpha lipoic acid (ALA) reduces the formation of reactive oxygen species (ROS) by directly scavenging free radicals, including hydroxyl radicals and hydrogen peroxide. Additionally, ALA chelates transition metal ions, preventing the conversion of weak oxidants into more harmful reactive species. ALA also enhances the levels of intracellular antioxidants such as glutathione, which further helps in neutralizing ROS. Moreover, ALA can regenerate other antioxidants like vitamin C and vitamin E, thereby maintaining a robust antioxidant defense system within the cell. Figure 10 was generated using BioRender.

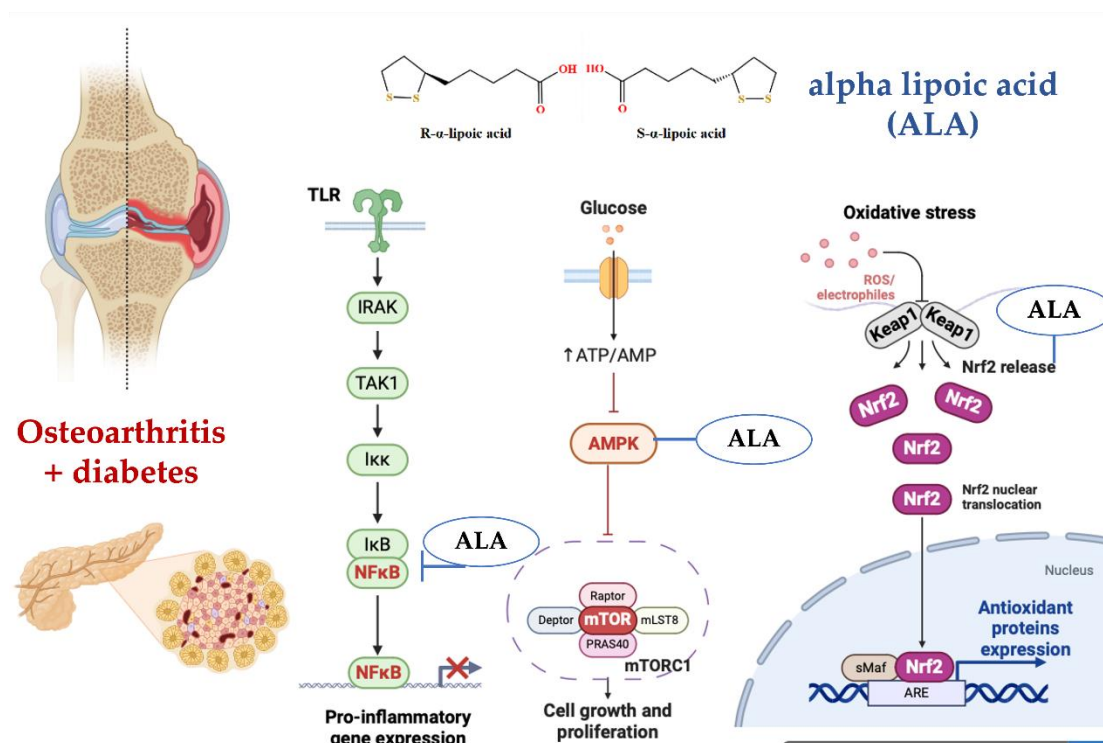


Figure 11. (Left) Alpha lipoic acid (ALA) has been shown to inhibit the NF-κB signaling pathway in various ways. Firstly, ALA pretreatment of human large artery endothelial cells (HAEC) significantly inhibited NF-κB binding activity induced by TNF-α in a dose-dependent manner, suggesting a metal chelation effect rather than a general antioxidation effect. Secondly, ALA has been demonstrated to block NF-κB activation, which is crucial for preventing the spread of influenza virus by inhibiting the virus-induced increase in NF-κB and caspase activities. Lastly, ALA can reduce the production of pro-inflammatory cytokines by negatively regulating NF-κB, thereby modulating the immune response and reducing inflammation. **(center)** Alpha lipoic acid (ALA) activates the AMPK pathway, which in turn inhibits the mTOR signaling pathway, leading to reduced cell growth and proliferation. Additionally, ALA-induced AMPK activation results in the phosphorylation and inhibition of mTOR, thereby promoting autophagy and improving cellular energy metabolism. **(right)** The Keap1-Nrf2 pathway is a signaling pathway involved in cellular responses to oxidative stress. The regulatory protein Keap1 regulates the activity of the transcription factor Nrf2. Under conditions of oxidative stress, Nrf2 is released from Keap1 and translocates to the nucleus, where it activates the expression of genes encoding antioxidant enzymes. Alpha lipoic acid (ALA) activates the Keap1-Nrf2 signaling pathway by modifying Keap1, leading to the release and nuclear translocation of Nrf2, which enhances the expression of antioxidant response element (ARE)-driven genes. This activation helps in reducing oxidative stress and promoting cellular defense mechanisms. Figure 11 was generated using BioRender.

The current research extends these findings by showing that ALA supplementation not only enhances glycemic control but also reduces joint dysfunction and inflammatory markers in patients with comorbid OA and T2DM. These results are consistent with other studies that have highlighted the potential of antioxidants in managing both metabolic and degenerative joint diseases [71–73].

However, the findings regarding ALA must be interpreted with caution. While the improvements observed in this study are promising, they are consistent with earlier reports that emphasize the need for further investigation into the long-term effects and optimal dosing of ALA in patients with multiple comorbidities [74–76]. Other studies have pointed out the variability in patient responses to ALA, which may depend on factors such as disease severity, duration of diabetes, and individual differences in metabolism [77–80]. The current study's relatively short duration and limited sample size suggest that more extensive research is needed to confirm these preliminary

results and to explore the potential mechanisms underlying ALA's effects in this specific patient population.

This study emphasizes the complex and multifaceted nature of comorbid OA and T2DM, highlighting the need for comprehensive and personalized treatment strategies. While the potential of alpha-lipoic acid as a therapeutic agent appears promising, further research is essential to fully understand its efficacy, safety, and long-term benefits in patients with both OA and T2DM.

6. Limitations

We acknowledge several limitations in our study. First, the relatively small sample size limits the generalizability of our findings to a wider population. A larger, multicenter study is necessary to validate these results and enhance their applicability. Additionally, the monocentric design of this study inherently restricts the population studied and may introduce selection bias. Future research should include participants from multiple centers to obtain a more representative sample. Moreover, the parameters investigated were not analyzed in a cohort of patients with T2DM who do not have comorbid OA.

5. Conclusions

This study demonstrates that the presence of type 2 diabetes mellitus in patients with osteoarthritis significantly exacerbates clinical symptoms and biochemical markers. Patients with osteoarthritis and type 2 diabetes exhibited elevated levels of inflammation, oxidative stress, and immunological disturbances compared to those with osteoarthritis. Additionally, the research identified significant correlations among metabolic, psychological, and inflammatory factors, highlighting the complex interactions between these elements in individuals with comorbid osteoarthritis and type 2 diabetes mellitus. The study also pinpointed potential predictors of this comorbidity. Integrating alpha-lipoic acid into the treatment regimen led to notable improvements, including reductions in joint dysfunction, CRP levels, and oxidative stress markers, alongside better glycemic control. However, further investigation is required to comprehensively evaluate the therapeutic potential of alpha-lipoic acid and its long-term effects. This research emphasizes the necessity for tailored treatment approaches to address the multifaceted challenges faced by patients with both osteoarthritis and type 2 diabetes mellitus.

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Data Availability Statement: Data are contained within the article.

Conflicts of Interest: The authors declare no conflicts of interest.

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