Diabetes Mellitus Are Less Likely to Aortic Dissection: A 5-Year Single-Center Analysis on independent risk factors of Aortic Dissection in Diabetes Mellitus Patients

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Abstract

Background

Diabetes mellitus (DM) is a severe risk factor in most cardiovascular diseases, but is negatively associated with the incidence of acute aortic dissection (AAD). The purpose of this study was to explore the independent risk factors for DM patients who are still with AAD and to establish a nomogram model to predict the risk of AAD in DM patients.

Methods

Clinical data on 364 DM patients who got surgical indications was collected from January 2016 to December 2021. These patients were divided into negative and positive cohorts according to the diagnosis of AAD. The logistic proportional hazards model was used to find out the risk factors related to DM patients with AAD. A nomogram was generated based on the contribution weights of the independent risk factors. AD mice model was constructed to verify related risk factors in vivo.

Results

Among 364 patients, AAD occurred in 25 (6.87%) patients. Multivariable logistic regression analysis showed that, after adjusting for confounders, preoperative LDH, hypertension, BMI, and coronary heart disease (CHD) were all positively associated with the risk of AAD in DM patients. (LDH: OR:1.003, 95% CI: 1.001–1005, p = 0.002; CHD: OR:3.591, 95% CI: 1.142–11.289, p = 0.029; Hypertension: OR:2.854, 95% CI: 1.087–7.494, p = 0.033; BMI: OR:1.184, 95% CI: 1.029–1362, p = 0.018). Pharmacological inhibition of LDH in AAD mice was able to decrease the incidence of AAD from 43.75–13.33%.

Conclusion

DM patients were negatively associated with AAD, but dysregulated preoperative-LDH BMI hypertension and CHD are risk factors for AAD in DM patients.

Introduction

As compared to non-diabetics, patients with DM carry a higher risk of cardiovascular disease across different ethnic groups and sex[1]. AAD, a fatal cardiovascular emergency, was characterized by an intimal tear and propagation of the dissection between the media and intimal of ascending aorta[2]. Although many patients with AAD have been rescued in time with the continuous improvement of diagnosis and surgical techniques, the incidence of AAD remains high. And there is no specific and effective method for early diagnosis and treatment at present. Interestingly, from clinical observation, we found a low prevalence of DM among AAD patients. There was a comprehensive literature search by

Tsai[3] identified a retrospective cohort study with 12 years of follow-up which demonstrated that negative association of DM with probable rupture of AAD, and strengthened our present observations. Based on the understanding of the correlation between DM and AAD, DM may be considered a protective factor during the development of AAD. In order to obtain a more comprehensive understanding of the prevention of AAD, we wanted to explore the independent risk factors for DM patients who are still with AAD. Therefore, the aim of our study was to explore the risk factors that are responsible for AAD in DM patients.

Hypertension, obesity, and CHD were common causes of AAD. Long-term elevated blood pressure promotes collagen deposition and increases vascular stiffness and the risk of tearing. And AAD patients in the presence of coronary-malperfusion have almost two times higher mortality than AAD patients without any complications. Lactate dehydrogenase (LDH) is a key enzyme in aerobic glycolysis, catalyzing the formation of pyruvate to lactate[4–6]. Numerous studies have shown the involvement of LDH in the development of cardiovascular diseases, including energy metabolism under the angiogenic process, atherosclerosis, and vascular remodeling in pulmonary hypertension[7]. Therefore, LDH may play a crucial role in the pathogenesis of cardiovascular diseases. We quantified and analyzed the values of the risk of AAD in DM patients to provide assistance for early prevention. In addition, we also made an AAD mice model with pharmacological inhibition of LDH and observed the survival index of mice to verify the influence of LDH on AAD.

Materials And Methods

Patients

From June 1, 2016, to December 2021, we retrospectively examined 364 DM patients with surgical indicators at Fujian Medical University Union Hospital. The inclusion criteria were as follows: (1) age ≥ 18 years, (2) diagnosed as type II diabetes mellitus, (3) AD diagnosed by CTA, (4) chest pain and other symptoms occurring within 14 days of diagnosis, and (5) emergency surgery performed 48 hours after admission. The exclusion criteria were as follows: (1) AAD caused by trauma, (2) pregnant women, (3) patients with onset of symptoms for more than 14 days, and (4) patients younger than 18 years of age. The Ethics Committees and Review Board of Fujian Medical University Union Hospital approved the study.

Data Collection

Patients were categorized into the negative group and the positive group according to whether there was diagnosed with AAD. The following variables were extracted from the database: gender, age, height, weight, and relevant medical history such as smoking, alcohol consumption, hypertension, diabetes, CHD, COPD, Marfan syndrome, history of cardiac surgery; and preoperative variables included: pericardial effusion, EF value, red blood cell (RBC) count, D-dimer value, white blood cell (WBC) count, hemoglobin,

platelet count, prothrombin time (PT), activated partial thromboplastin time (APTT), prothrombin time (TT), fibrinogen (FIB), TBIL, albumin, ALT, AST, γ-glutamyl transpeptidase, ALP, serum creatinine, urea, LDH.

Ad Mouse Model

C57BL/6J male mice were divided into three groups. The control group (n = 10) was fed normally, and the AD model group (n = 16) and Oxamate (Inhibitor of LDH-A) group (n = 15) were fed with drinking water containing 0.3% BAPN (A0408, TCI) for 5 weeks. The Oxamate group was also fed with 0.3% BAPN in drinking water and daily intraperitoneal injection of Oxamate 500 mg/kg (s30701-5g, Yuanye Biotechnology). On the 35th day, Ang II (4474-91-3, Tocris) was subcutaneously injected with a total dose of 1.44 mg/kg, divided into 5 times with an interval of 1 h. The AD model was improved based on the reported literature[8]. Instead of using the subcutaneous sustained-release pump, we administered Ang II with multiple subcutaneous injections, which alleviated the pain of the mice. The dosage, mode, and interval of administration of Oxamate were determined according to previous studies[9]. Fasting glucose concentration (FGC) was measured using reagent strips read in a glucose meter (YSI 2300-STAT), and SIC was measured using mouse insulin (INS) ELISA-kits (CSB-E05071m, CUSABIO, China) by the tail-cuff method after grouping and before implantation.

Western Blot

Western blot
Total proteins were isolated using cell lysis buffer (Beyotime Institute of Biotechnology, Shanghai, China). Protein extracts were separated by sodium dodecyl sulfate-polyacrylamide gel electrophoresis (SDS-PAGE; 8–12%) and then transferred to polyvinylidene difluoride (PVDF) membranes. Next, PVDF membranes were blocked with 5% skimmed milk in PBS (0.05%) Tween 20 for 2 h at room temperature. Quantification was assessed by Image J.

Statistical Analysis

The statistical analysis was performed using IBM SPSS Statistics (version 22.0 Inc., Chicago, IL, USA) and the R programming language (version 3.4.1, Vienna, Austria). Data are reported as the means and medians with percentages. The chi-square test and Student's t-tests were performed in univariate analysis to determine the differences in parameters between the two groups. Factors found to be significant ($P < 0.050$) in univariate analysis were included in the subsequent multivariate logistic regression analysis to identify the independent risk variables associated with AAD in DM patients[10]. The nomogram was constructed based on the results of the multivariate analysis and evaluated by the receiver operating characteristic (ROC) curve, the area under the ROC curve (AUC), and the calibration curve. The odds ratio (OR) and 95% confidence interval (CI) were calculated. P value < 0.05 was considered statistically significant.

Results

Patients Characteristics

The 364 DM patients with surgical indicators were all Asian and were divided into two groups (positive and negative) according to the diagnosis of AAD. The positive group included 25 (6.87%) patients. DM patients diagnosed with AAD in the positive group underwent surgery within 48 hours. There was no significant difference in the sex of the included patients, and the mean age was 52.81 ± 10.80 years. Patients in the positive group were older compared to the negative group ($p = 0.0292$) and had significantly higher BMI values compared to the negative group ($p < 0.001$). According to the current grading criteria for hypertension[11], we classified the included patients into 3 stages of hypertension. AAD occurred in a much higher percentage of DM patients with concomitant hypertension (96%) than in the negative group (5.01%, $p < 0.001$). Stage 1 hypertension plays a more important role in promoting the development of AAD. In addition, according to the grading of coronary artery stenosis[12], coronary stenosis (< 50%) was more common in the positive group ($p < 0.001$). Observation of patients' preoperative surgical indicators revealed that LDH levels were significantly higher in the blood of patients in the positive group (439.92 ± 295.59 U/L) compared to the negative group (296.16 ± 259.41 U/L) ($p = 0.008$). There were no statistically significant differences in other variables (Table 1).

Table 1. Univariate analysis of possible risk factors for patients with diabetes mellitus type 2

Variable	All patients, N=364	AD		P value
		Negative, N=339	Positive, N=25	
Sex				0.0859
Male	181 (49.73%)	169 (49.85%)	12 (48.00%)	–
Female	183 (50.27%)	170 (50.15%)	13 (52.00%)	–
Age (years)	52.81±10.80	52.64±10.77	55.00±11.24	0.0292
Height (cm)	170.62±9.17	170.89±9.09	167.00±9.65	0.040
Body Weight (kg)	73.54±13.52	73.17±13.54	73.27±13.68	0.677
BMI	25.28±4.35	25.06±4.40	28.12±3.09	**<0.001**
Medical history (%)				
Drunk	96 (26.37%)	87 (25.66%)	9 (36.00%)	0.259
Smoke	167 (45.88%)	155 (45.72%)	12 (48.00%)	0.826
Heart Surgery	43 (11.81%)	38 (11.21%)	5 (20.00%)	0.302
Hypertension	41 (11.26%)	17 (5.01%)	24 (96.00%)	**<0.001**
Level 1	23 (6.31%)	6 (1.77%)	17 (68.00%)	–
Level 2	12 (3.29%)	7 (2.06%)	5 (20.00%)	–
Level 3	6 (1.65%)	4 (1.18%)	2 (8.00%)	–
Marfan	20 (5.49%)	20 (5.90%)	5 (20%)	0.100
COPD	23 (6.32%)	21 (6.19%)	2 (8.00%)	0.721
CHD	33 (9.06%)	10 (2.95%)	23 (92.00%)	**<0.001**
Level 1	24 (6.59%)	4 (1.18%)	20 (80.00%)	–
Level 2	3 (0.82%)	2 (0.59%)	1 (4.00%)	–
Level 3	6 (1.65%)	4 (1.18%)	2 (8.00%)	–
Preoperative Indexes				
ALT(U/L)	32.60±21.82	32.12±21.49	39.08±25.47	0.124
CR (μmol/L)	81.34±112.88	83.79±116.14	48.21±39.00	0.128
HB	118.58±23.72	118.89±23.03	114.29±31.90	0.349
EF ($\bar{x}$±s, %)	65.00±8.65	65.04±8.52	64.48±10.48	0.756
DD (μg/ml)	12.75±7.56	12.89±7.63	10.78±6.26	0.119

PLT	194.75±74.26	194.79±75.07	194.16±63.61	0.967
PT	16.77±3.90	16.80±3.91	16.30±3.77	0.538
RBC	6.93±0.76	6.92±0.77	7.05±0.61	0.368
ALB	39.09±6.38	39.03±6.38	40.02±6.35	0.454
APTT	35.62±8.76	35.62±8.59	35.61±10.99	0.997
TT	20.47±24.53	19.78±22.37	29.82±22.37	0.272
FIB	3.63±1.96	3.64±1.97	3.48±1.80	0.687
DBIL	6.53±7.50	6.55±7.69	6.32±4.31	0.887
IBIL	14.89±10.58	14.82±10.63	15.85±9.90	0.641
WBC	11.08±4.14	11.15±421	10.16±2.88	0.250
AST	32.70±19.53	32.64±19.50	33.48±30.19	0.836
GGT	44.99±34.69	44.58±34.41	50.48±38.63	0.483
BNP	1099.49±2460.23	1121.60±2535.14	799.68±966.68	0.529
TBLT	18.12±17.57	18.11±17.89	18.16±12.67	0.991
LDH	306.04±264.12	296.16±259.41	439.92±295.59	**0.008**
UREA	7.03±3.84	7.13±3.89	5.59±2.70	0.053
Na^+	138.66±3.63	138.60±3.65	139.57±3.27	0.198
K^+	3.60±0.66	3.61±0.67	3.55±0.52	0.683
Ca^{2+}	2.26±0.16	2.27±0.16	2.23±0.22	0.365

BMI=body mass index; COPD=Chronic Obstructive Pulmonary Disease; CHD=Coronary Heart Disease; ALT=Alanine Transaminase ; CR=Creatinine ; HB=Hemoglobin; EF=Ejection Fraction; DD= D-Dipolymer ; PLT=Platelet ; PT=Prothrombin Time ; RBC=Red Blood Cell ; ALB=Albumin ; APTT=Activated Partial Thromboplastin Time ; TT=Thrombin Time ; FIB=Fibrinogen ; DBIL=Direct Bilirubin ; IBIL=Indirect Bilirubin ; WBC=White Blood Cell ; AST=Aspartate Transaminase ; GGT=Glutamyl Transpeptadase ; BNP= Brain Natriuretic Peptide;TBIL=Total Bilirubin; LDH= Lactate Dehydrogenase; Cl=Confidence interval; OR=odds ratio.

The Risk Factors Of Dm Patients With Aad

The summary of univariate logistic regression analysis was shown in Table 2. BMI, Marfan, hypertension, CHD, and LDH were risk indicators for the development of AAD in DM patients (BMI, $p < 0.001$, Marfan, $p = 0.012$, hypertension, $p < 0.001$, CHD, $p < 0.001$, LDH, $p = 0.011$, respectively). The multifactorial logistic

regression analysis (Table 3) including the above risk indicators was established. The results showed that the independent risk factors for the development of AAD in DM patients were BMI (OR = 1.184, 95% CI: 1.029–1.362, p = 0.018), LDH (OR = 1.003, 95% CI: 1.001–1.005, p = 0.002), and hypertension (OR = 2.854, 95% CI: 1.087–7.494, p = 0.033) and coronary artery disease (OR = 3.591, 95% CI: 1.001–1.005, p = 0.002).

Table 2
Univariate analysis of possible risk factors for DM patients with AD

Characteristic	B	OR	95%CI	P value
BMI	**0.161**	**1.174**	**1.066–1.293**	**< 0.001**
Age	0.074	1.021	0.478–2.428	0.858
Year(s)	0.02	1.001	0.983–1.060	0.292
Smoke	0.091	1.096	0.486–2.471	0.826
Drink	0.488	1.629	0.695–3.821	0.262
Heart Surgery	0.683	1.980	0.702–5.583	0.196
Hypertension	**1.866**	**6.465**	**3.742–11.169**	**< 0.001**
LDH	**0.002**	**1.002**	**1.000-1.003**	**0.011**
Marfan	**1.383**	**3.987**	**1.355–11.731**	**0.012**
COPD	0.275	1.317	0.291–5.966	0.721
CHD	**2.274**	**9.722**	**4.340-21.777**	**< 0.001**
EF	-0.007	0.993	0.949–1.040	0.772
RBC	0.167	1.181	0.638–2.186	0.595
DD	-0.039	1.845	0.908–1.018	0.174
WBC	-0.058	0.994	0.852–1.044	0.262
HB	0.001	1.001	0.991–1.011	0.847
PLT	-0.001	1.000	0.994–1.005	0.967
PT	-0.035	0.996	0.848–1.099	0.598
APTT	0.001	1.001	0.956–1.048	0.964
TT	0.009	1.009	0.999–1.019	0.078
FIB	-0.033	0.968	0.781–1.198	0.763
BNP	-0.002	1.000	0.880–1.050	0.536
TBLT	0.002	1.000	0.978–1.023	0.985

BMI = body mass index; COPD = Chronic Obstructive Pulmonary Disease; CHD = Coronary Heart Disease; ALT = Alanine Transaminase ; CR = Creatinine ; HB = Hemoglobin; EF = Ejection Fraction; DD = D-Dipolymer ; PLT = Platelet ; PT = Prothrombin Time ; RBC = Red Blood Cell ; ALB = Albumin ; APTT = Activated Partial Thromboplastin Time ; TT = Thrombin Time ; FIB = Fibrinogen ; DBIL = Direct Bilirubin ; IBIL = Indirect Bilirubin ; WBC = White Blood Cell ; AST = Aspartate Transaminase ; GGT = Glutamyl Transpeptadase ; BNP = Brain Natriuretic Peptide;TBIL = Total Bilirubin; LDH = Lactate Dehydrogenase. CI = Confidence interval; OR = odds ratio.

Characteristic	B	OR	95%CI	P value
ALB	0.022	1.023	0.964–1.085	0.456
ALT	0.013	1.013	0.996–1.029	0.128
AST	0.002	1.002	0.982–1.023	0.835
GGT	0.004	1.004	0.994–1.015	0.413
UREA	-0.150	0.861	0.742–0.999	0.149
CR	-0.014	0.986	0.974–0.999	0.140
IBIL	0.008	1.008	0.974–1.042	0.663
DBIL	-0.005	0.995	0.939–1.055	0.875
Na^+	0.077	1.080	0.959–1.216	0.204
K^+	-0.314	0.730	0.388–1.376	0.330
Ca^{2+}	-0.074	0.929	0.168–5.147	0.932

BMI = body mass index; COPD = Chronic Obstructive Pulmonary Disease; CHD = Coronary Heart Disease; ALT = Alanine Transaminase ; CR = Creatinine ; HB = Hemoglobin; EF = Ejection Fraction; DD = D-Dipolymer ; PLT = Platelet ; PT = Prothrombin Time ; RBC = Red Blood Cell ; ALB = Albumin ; APTT = Activated Partial Thromboplastin Time ; TT = Thrombin Time ; FIB = Fibrinogen ; DBIL = Direct Bilirubin ; IBIL = Indirect Bilirubin ; WBC = White Blood Cell ; AST = Aspartate Transaminase ; GGT = Glutamyl Transpeptadase ; BNP = Brain Natriuretic Peptide;TBIL = Total Bilirubin; LDH = Lactate Dehydrogenase. CI = Confidence interval; OR = odds ratio.

Table 3
Multivariate analysis of independent risk factors for DM patients with AD

Characteristic	B	OR	95%CI	P value
BMI	0.169	1.184	1.029–1.362	0.018
Marfan	1.386	4.000	0.821–19.475	0.086
Hypertension	1.049	2.854	1.087–7.494	0.033
LDH	0.003	1.003	1.001–1.005	0.002
CHD	1.278	3.591	1.142–11.289	0.029

BMI = body mass index; CHD = Coronary Heart Disease; LDH = Lactate Dehydrogenase. CI = Confidence interval; OR = odds ratio.

Nomogram

A nomogram was constructed to predict the risk of AAD in DM patients, including four significant independent risk factors: stage of hypertension, coronary diseases, LDH, and BMI. The total score was

obtained by summing up the single scores used to estimate the probability of AAD in DM patients and illustrate the relative contribution of each risk factor to the overall risk (Fig. 1). Calibration curve of nomogram model (1-year overall survival of this population). The x-axis and y-axis represent the predicted 1-year survival probability and the actual survival probability of the nomogram model, respectively (Fig. 2). The the ROC curve was shown in Fig. 3, with an AUC (c-index) of 0.793.

Ldh-a Inhibitor Affected Blood Glucose Of Ad Mice And Alleviated Ad Progression

Our results demonstrated the upregulation of LDH-A expression in the aortic tissue of AD mice (n = 8) (Fig. 4). We used Oxamate to pharmacologically inhibit LDH-A expression in mice (Group 2)[9]. Oxamate improved the survival rate (86.67% vs 56.25%, p = 0.025) in AD mice (Group 1) (Fig. 5). At week 5 of modeling, body weight was 17.3 ± 3.22 g, and blood glucose was 8.0 ± 2.64 mmol/L in group 1. The body weight (Figs. 6) of group 2 was 20.1 ± 1.20 g, and blood glucose (Fig. 7) was 6.8 ± 1.34 mmol/L. The results indicated that LDH-A, as a key enzyme of glycolysis, could influence the blood glucose and body weight of mice.

Discussion

With the advances in diabetes care, the trend of incident cardiovascular disease in DM patients has been decreasing over the past decades. However, cardiovascular diseases were also the leading cause of death in DM patients, and the risk of cardiovascular diseases in DM patients is more than twice that of non-DM patients[13]. Interestingly, our current results demonstrated that the incidence of AAD was only 6.87% in DM patients with surgical indicators. Previous studies have provided evidence for the negative association of DM with the presence, growth, and probably rupture of aortic aneurysm (AA). Tsai et al[14] identified that, compared with 646, 710 comparison patients, 160, 391 DM patients were significantly and independently associated with reduced AA without rupture (adjusted hazard ratio [HR] of 0.50; 95% CI, 0.35–0.71; P < 0.001). Uncomplicated DM patients trended to be associated with reduced AA without rupture (adjusted HR, 0.85; 95% CI, 0.63–1.16). There was a retrospective study by Theivacumar et al[15] reported that among 2062 patients with AAA/AAD, 12.3% of the 1830 patients with AA were diabetic; however, only 5.6% of the 232 patients with AD were diabetic (OR, 0.42; 95% CI, 0.23–0.75; P < 0.004).

Based on the negative association between DM and AA/AAD, we retrospectively analyzed DM patients with cardiac surgery indications in our hospital in the last decade. And we found a similar conclusion that DM also negatively regulates the incidence of AAD. The pathophysiological basis of the inverse association between DM and AAD can be explained by the fact that hyperglycemia alleviated AAD by inhibiting the activation of immune cells, matrix metalloproteinase (MMP) activity, vascular smooth muscle cell (SMC) phenotype transformation and reducing neovascularization[16–18]. Firstly, DM patients have reduced levels and activity of matrix metalloproteinase (both MMP-2 and MMP-9), which inhibited the degradation and remodeling of ECM in the aortic wall; secondly, large amounts of advanced

glycosylation end products (AGEs) were produced in DM patients in vivo; lastly, fibrinolytic enzyme activity was also inhibited in vivo. The all factors above were closely associated with increased aortic wall stiffness.

Based on the understanding of mechanisms between DM and AAD, DM may have a protective role in the development of AAD. However, there still exists some DM patients with AAD. We further investigated the risk factors that clinically induce the development of AAD in patients who were diagnosed with DM. The results of the univariate and multifactorial logistic analysis showed that LDH, hypertension, BMI, and CHD were identified as risk factors for the development of AAD in DM patients. Hypertension is known to be the most common cause of AAD. Prolonged elevated blood pressure (BP) leads to SMCs degeneration and the production of MMPs, which makes it more susceptible to vascular tearing[19, 20]. A population-based prospective study found that 67.3% of patients with AAD were diagnosed with hypertension. Proportional analysis showed that the subsequent BP of 61.9% of patients was higher than 140/90 mmHg, despite the majority of patients having received combined anti-hypertensive therapy[21]. In addition, patients with AAD who died immediately had significantly higher premorbid systolic BP than those who survived hospital admission (151.2 ± 19.3 vs 137.9 ± 17.9 mmHg; $p < 0.001$)[22]. These results indicated that uncontrolled hypertension was associated with the incidence of AAD. In our study, 25 patients were diagnosed with DM and developed AAD, 24 of whom had different stages of hypertension (96%). AAD was more common in DM patients with severe hypertension than in non-hypertension DM patients (96.00% vs 5.01%). Therefore, even though diabetes may function as a protective role in AD, the incidence of AD remains high in the presence of diabetes complicated with hypertension.

In addition to hypertension, CHD may also play an essential role in the development of AAD in DM patients. Logistic regression analysis showed that CHD is associated with the risk of AAD in DM patients. It is noteworthy that both CHD and AAD can be caused by the same causative factors, such as hypertension. Hypertension can lead to the development of AAD and coronary vascular endothelial damage which promotes the formation of CHD[23]. A similar symptom between AAD and CHD was severe pain in the precordial region, which was the most predominant manifestation. Furthermore, AAD may induce coronary artery dissection and then trigger a coronary heart attack. It's known that atherosclerosis is the underlying cause of most cardiovascular diseases, which involve plaque formation, intimal thickening due to lipid deposition, inflammation, and arterial wall thickening. Rupture of unstable plaques can lead to atherosclerotic and severe clinical symptoms. It has been suggested that inherited genetic mutations in the aorta also played a role in the atherosclerotic process[24]. And some studies also reported that patients with inherited aortic lesions were negatively associated with atherosclerotic lesions, which was contrary to the results of our study. The explanation may be related to the selection of our study population, but it is undeniable that there is an association between CHD and AAD in DM patients.

Compared to non-DM patients, the level of glycolysis in DM patients was closely associated with aortic disease and was essential for aortic SMCs. L-lactic acid, as an end product of glycolysis, can serve as a substrate for mitochondrial reserve. Once there exists a supply-demand imbalance in energy demand, the

reserve capacity will be a potential source of energy supply to avoid cellular crises due to a lack of ATP [25, 26]. LDH-A is a key enzyme in glycolysis, encoded by the gene located on chromosome 11p15.1, which preferentially converts pyruvate to lactate. Recent studies have demonstrated that LDH-A has a close relationship with cardiovascular diseases and may be a potential therapeutic target for heart failure and pulmonary hypertension[27, 28]. It has also been demonstrated that LDH-A-driven lactate may create a microenvironment beneficial to cardiac regeneration[29]. These findings suggest that targeting metabolic reprogramming through LDH-A might be an effective protection strategy for cardiovascular diseases. To gain more insight into whether LDH-A can be involved in the development of AD by driving metabolic programming, we constructed a mouse model of AD. Under the inhibition of LDH-A by Oxamate, the incidence of AD was significantly downregulated, compared to the AD group. The fluctuation of blood glucose levels caused by the intervention of LDH-A may be due to the blockage of the glycolytic process in vivo. Complications resulting from dysregulated glucose metabolism can induce hyperlipidemic syndrome[30], thus there existed a close association between glucose and lipid metabolism. Our results showed that under the inhibition of LDH-A, the body weight of mice was changed significantly. Obesity is also one of the major risk factors for AAD[31]. Pathologically, the association between body mass index (BMI) and AD may be explained by the degeneration of the aortic medial wall being partly caused by inflammation referred from the peripheral vascular adipose tissue. We suggested that LDHA may influence the process of AD through glycolipid metabolism, and the exact mechanism would be further demonstrated in our subsequent experiments.

The risk factors we mentioned above and the nomograph prediction model constructed in this study can assist us to realize individualized risk prediction before AAD. Both clinicians and patients themselves can use these indicators to achieve early risk assessment of AD and then early intervention to obtain a better prognosis. This study also has some limitations. First, the sample size of this study is small, and it is a single-center retrospective study. Secondly, we only indirectly verified the function of LDH on AD, and more experimental evidence of the other factors would be required to determine the plausibility of our results. Future studies of AAD treatment should consider DM and the risk factors we mentioned above. Finally, we only used data from a case-control study though a retrospective cohort study. Therefore, more prospective, multi-center, and large-scale studies are needed to evaluate the value of the model in further studies.

Conclusion

DM may be negatively associated with the presence of AAD. However, hypertension, CHD, dysregulated preoperative LDH, and higher BMI remain high-risk factors for the development of AAD in DM patients.

Declarations

Ethics approval and consent to participate

This study was reviewed and approved by the Ethics Committee of Fujian Medical University Union Hospital (No. 2022KY031). The Ethics Committee of Fujian Union Medical College Hospital waived the need of written informed consent to participate in this study. All animal methods were carried out in accordance with relevant guidelines and regulations. And the animal experiments were approved by the Ethical Board of Fujian Union Medical College Hospital (No.2019-36).

Statements

All methods were carried out in accordance with relevant guidelines and regulations. And for animal experiments only, all methods are reported in accordance with ARRIVE guidelines (https://arriveguidelines.org) for the reporting of animal experiments.

Consent for publication

Not applicable.

Availability of data and materials

The data that support the findings of this study are available from Fujian Cardiac Medical Center but restrictions apply to the availability of these data, which were used under license for the current study, and so are not publicly available. Data are however available from Xi Yang and Ling Chen author upon reasonable request and with permission of Fujian Cardiac Medical Center.

Competing interests

All authors declare that they have no competing interests.

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Authors' Contributions

YX and CL conducted the study, participated in data collection, and drafted the manuscript. WJB and CKY participated in data acquisition, and chart production. It was reviewed and edited by CKY and CLW. All authors contributed to the interpretation of the data and the completion of the figures and tables, and read and approved the final manuscript.

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Figures

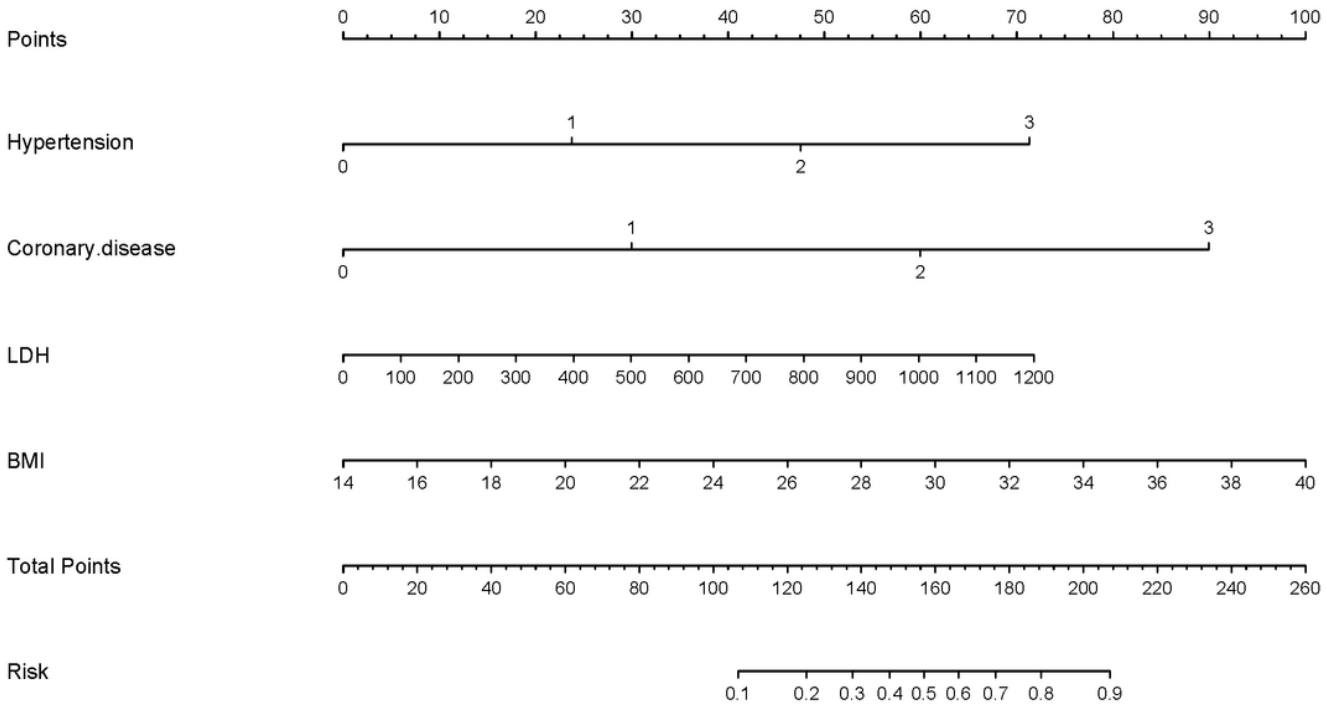

Figure 1

The nomogram prediction model of AAD risk in DM patients. The nomogram was established to predict the risk of AAD in DM patients. The total score can be calculated by summation of single scores. We can estimate the probability of AAD by projecting the total score to the lower total point scale.

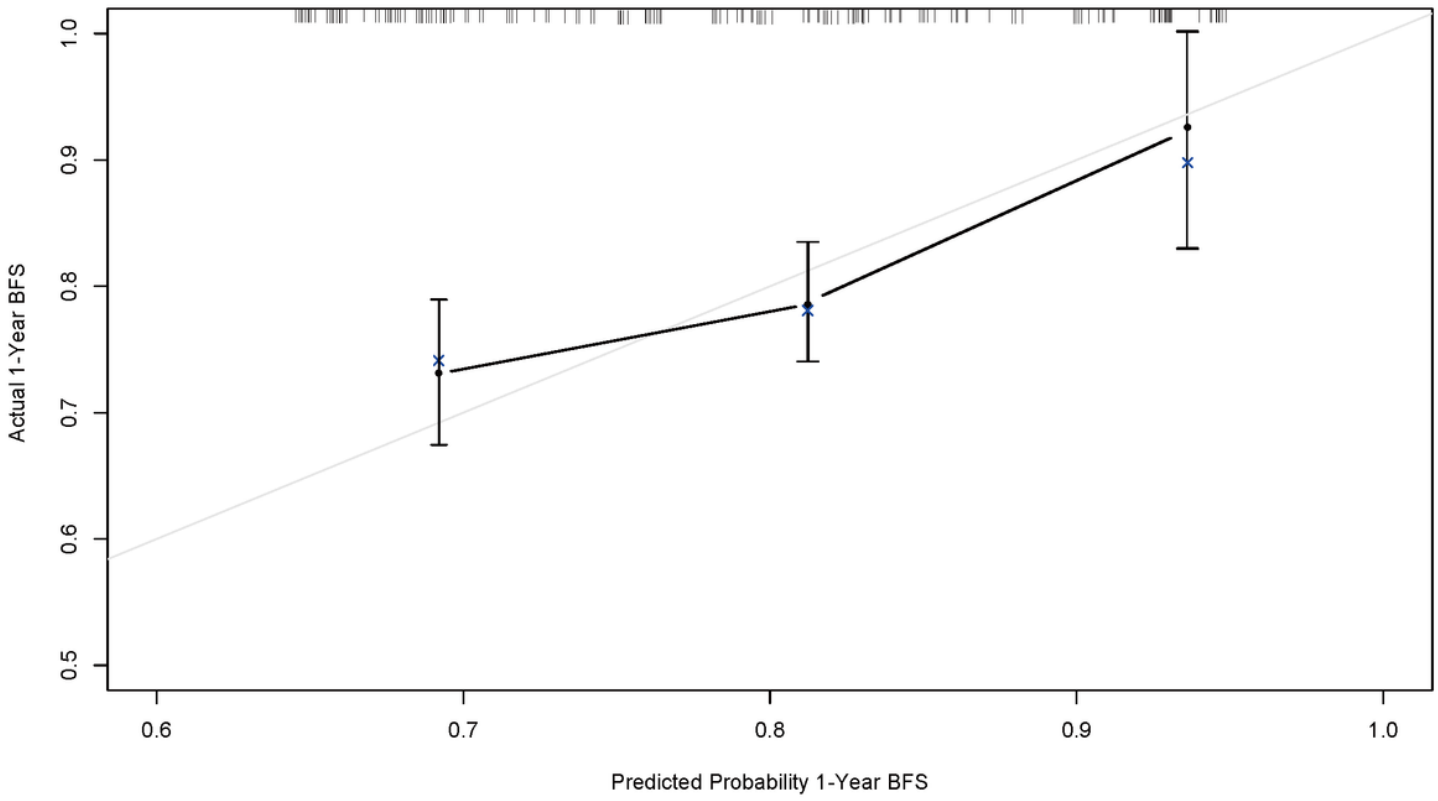

Figure 2

Calibration curves for the nomogram. The x-axis represents the nomogram-predicted probability, and the y-axis represents the actual probability of the nomogram. A perfect prediction would correspond to the 45◦ yellow dashed line.

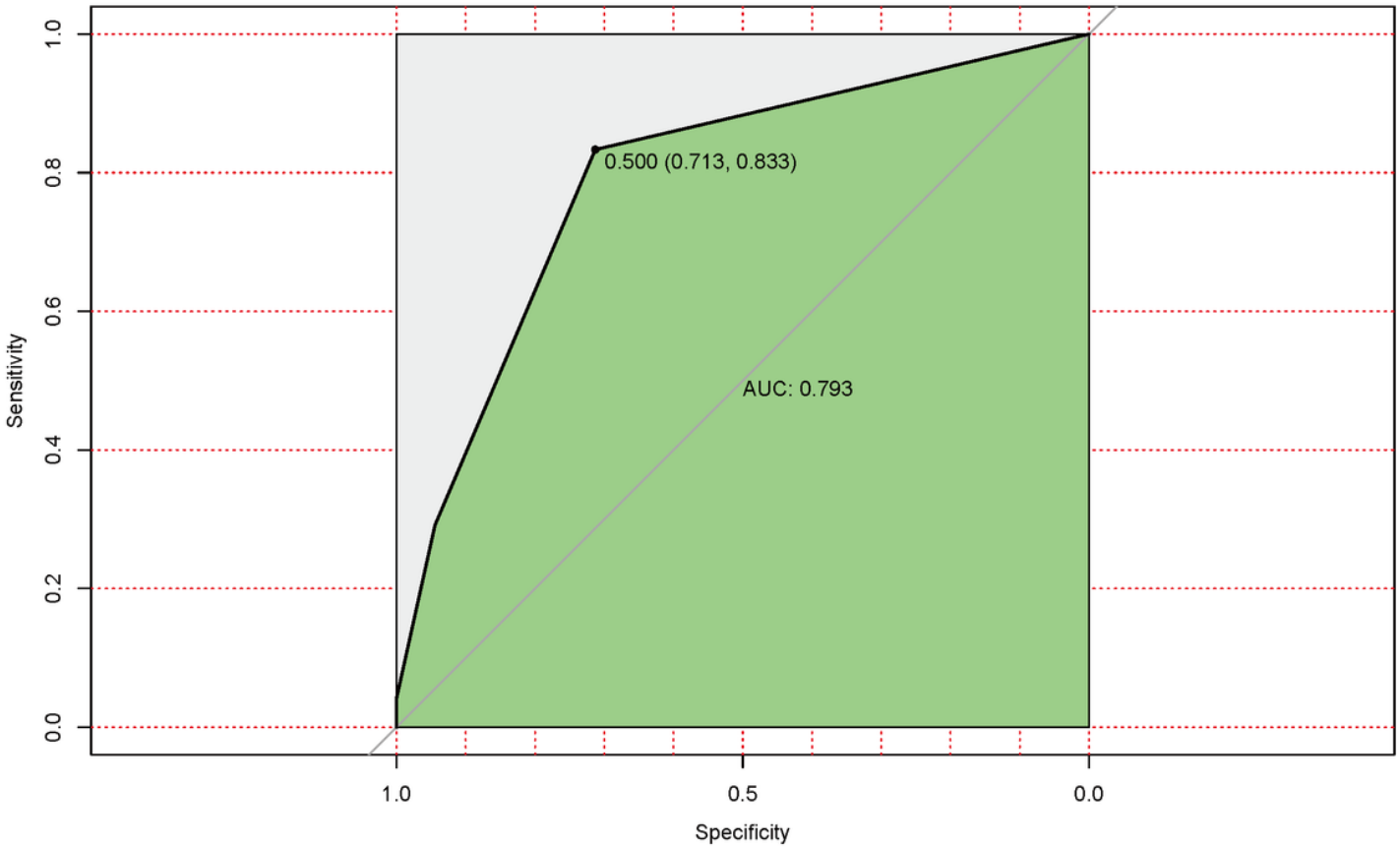

Figure 3

The receiver operating characteristic (ROC) curve for the nomogram. The C-index was 0.793 (95% CI: 0.766–0.820).

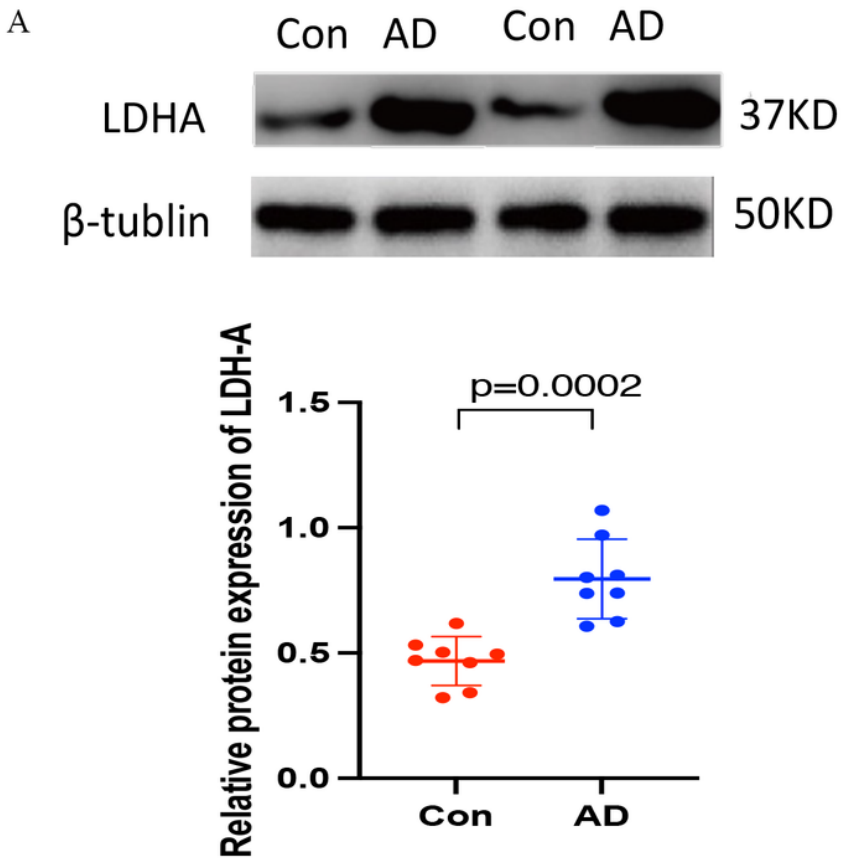

Figure 4

Relative protein expression of LDH-A in mice. The expression of LDHA in aota tissues of mice was detected by Western blot.

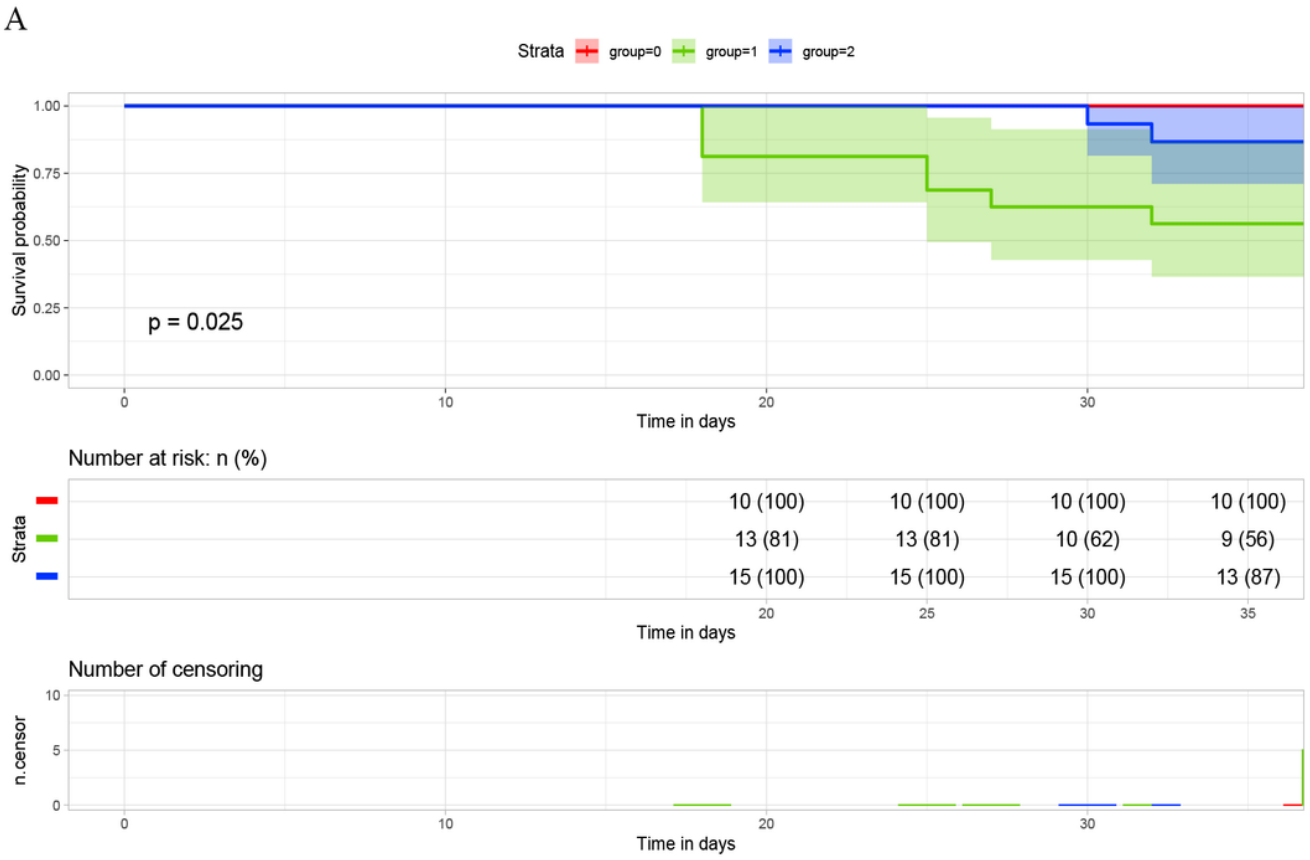

Figure 5

Survival rate of mice. Control group= group 0, AD group= group 1, AD group treated with Oxamate= group 2. Oxmate, pharmacological inhibition of LDH-A, was used in AD mice, and the survival rate was increased compared to mice in the AD group.

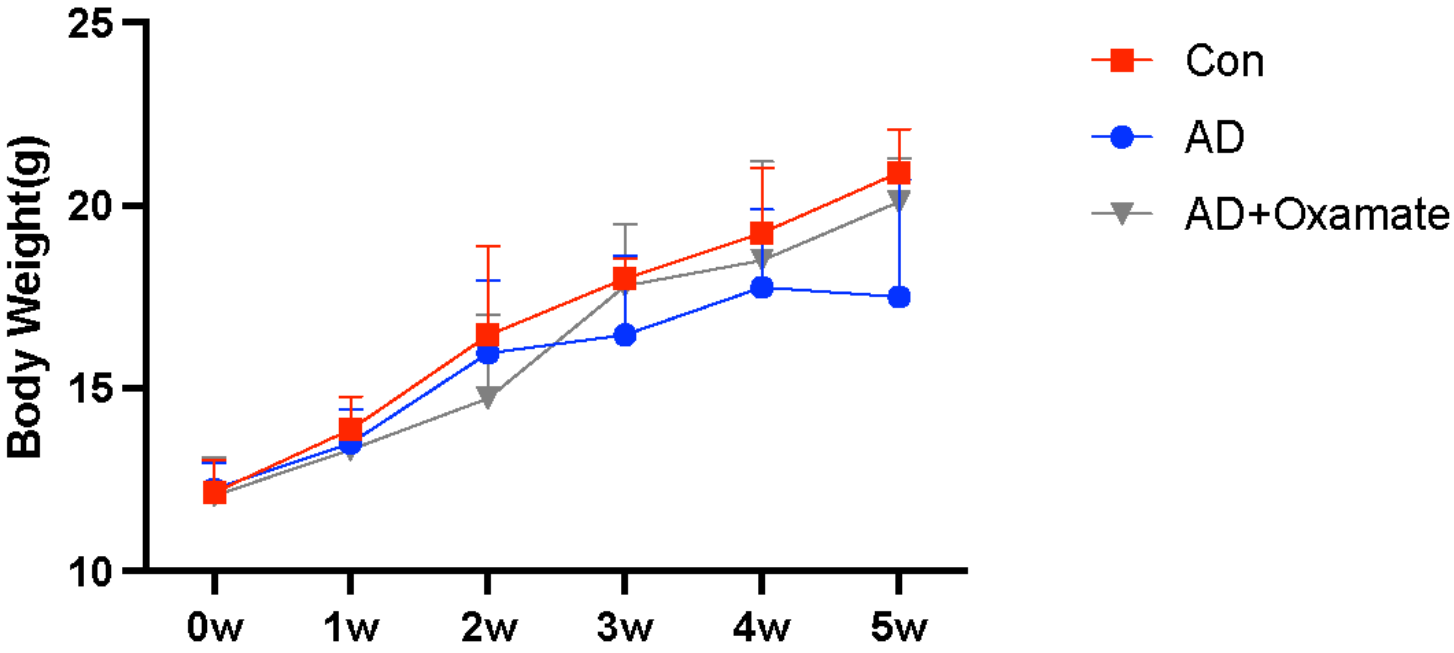

Figure 6

Body weight of mice. Body weight was of mice was collected every week in regular time.

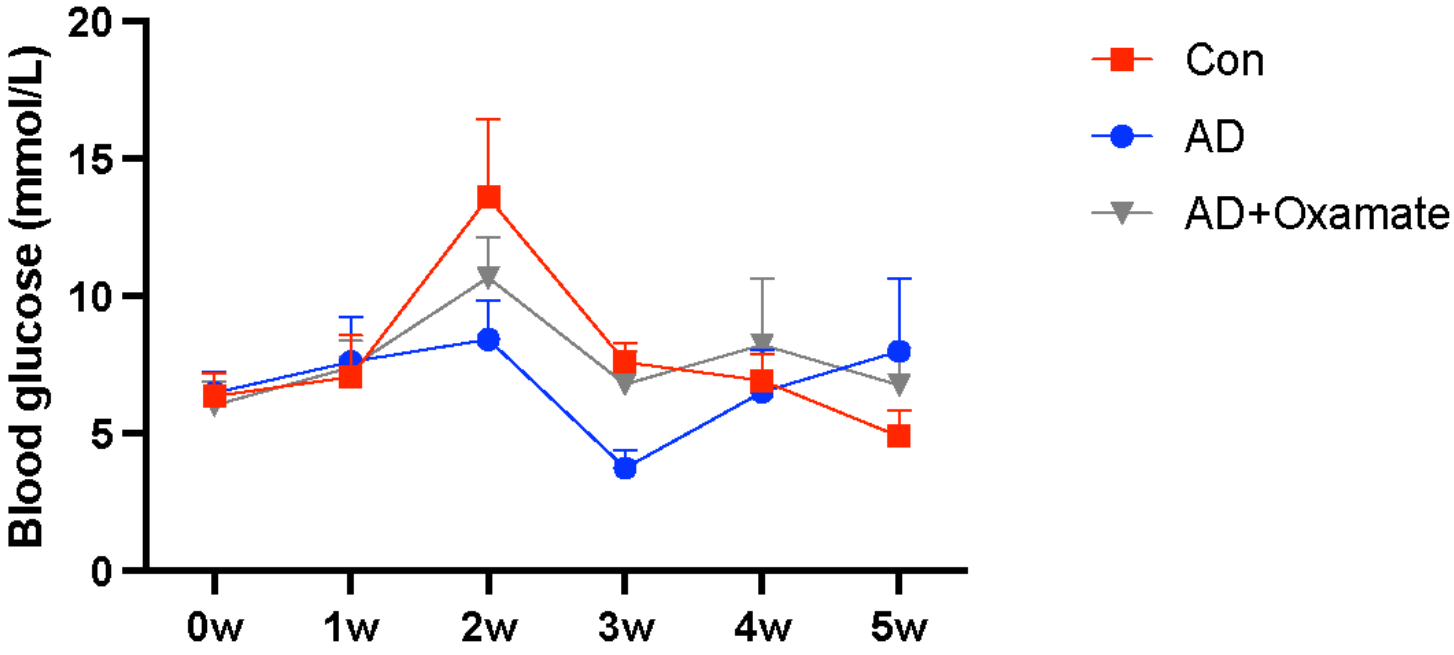

Figure 7

Blood glucose of mice. Blood glucose was of mice was collected every week. And Oxmate affected glucose significantly.

Supplementary Files

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