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Correlation between blood lactate level and cardiac function in patients with type 2 diabetes mellitus

QIAO Yan*, Li Jun, LI Qingju

** Zhengzhou University, Zhengzhou, Henan 450000, China*

Corresponding author: LI Qingju, E-mail:liqingju1133@163.com

Abstract: Objective To detect the blood lactate levels in patients with type 2 diabetes mellitus (T2DM) and analyze its correlation with various cardiac function indexes. **Methods** A cross-sectional study was conducted on 188 T2DM patients treated in the Department of Endocrinology, the Second Affiliated Hospital of Zhengzhou University from April to July 2023. Based on whether the blood lactate level was greater than 2.5 mmol/L, they were divided into T2DM+ elevated blood lactate group (n=100) and T2DM + normal blood lactate group (n=88). On the next day of admission, all enrolled patients underwent fasting venous blood tests for biochemical analysis, myocardial enzyme markers, and echocardiography to measure left ventricular ejection fraction (LVEF), left ventricular end-diastolic diameter (LVEDD), and other related cardiac function indexes. The correlations between blood lactate levels and cardiac function indexes in patients with T2DM were analyzed. **Results** Compared with the T2DM+normal blood lactate group, the T2DM+elevated blood lactate group was younger, and had a higher proportion of males (P< 0.05); Fasting blood glucose (FBG), glycated hemoglobin (HbA1c), insulin resistance index, triacylglycerol (TG), very low density lipoprotein cholesterol (VLDL-C) increased (P<0.05), and 25 hydroxyvitamin D [25-(OH) D] decreased (P< 0.05); LVEDD increased (P< 0.01), while LVEF decreased (P< 0.01). Spearman correlation analysis showed that blood lactate level was positively correlated with FBG, HbA1c, insulin resistance index, VLDL-C, TG, and LVEDD (r=0.204, 0.203, 0.213, 0.282, 0.324, 0.600, P<0.05), respectively; and negatively correlated with gender and LVEF (r=-0.172, -0.646, P<0.05), respectively; but not with age or 25-(OH) D (r=-0.131, -0.084, P>0.05). Multiple linear regression analysis showed that LVEF and LVEDD were influencing factors of blood lactate (P<0.05). **Conclusion** In patients with T2DM, an increase in blood lactate levels is associated with a decline in cardiac function.

Keywords: Type 2 diabetes mellitus; Blood lactate; Blood glucose; Cardiac dysfunction; Insulin resistance index

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Latest data show that type 2 diabetes mellitus (T2DM) accounts for over 90% of diabetes cases [1]. Plasma lactate concentration correlates with glycolytic rate, with mitochondrial oxidative capacity being critical to glycolytic rate [2]. In patients with T2DM, sustained hyperglycemia promotes the release of inflammatory factors, leading to chronic subclinical inflammation. This condition may impair mitochondrial function, affecting glycolytic rate and increasing the risk of lactate accumulation [3]. Skeletal muscle and myocardium are the primary tissues producing lactate. In cases of heart failure, impaired cardiac pumping can lead to inadequate circulatory blood volume, resulting in tissue hypoxia. In this scenario, glycolytic rate slows down, leading to increased lactate production and reduced metabolism in tissues and organs, thus causing lactate accumulation. Consequently, blood lactate levels in the body continue to rise, resulting in hyperlactatemia and potentially even lactic acidosis. Although research now indicates a relationship between lactate and T2DM, studies on the correlation between elevated lactate levels and heart failure in T2DM patients are limited. This study analyzes blood lactate levels and related factors in T2DM patients, and evaluates the correlation between blood lactate levels and heart failure.

1 Materials and methods

1.1 Study subjects

This cross-sectional study included 188 T2DM patients who visited The Second Affiliated Hospital of Zhengzhou University from April 2023 to July 2023. All patients underwent blood lactate testing and were divided into high lactate group (n = 100) and normal lactate group (n = 88) based on whether their blood lactate level exceeded 2.5 mmol/L. The study was approved by the Ethics Committee of The Second Affiliated Hospital of Zhengzhou University (Approval No. 2023081). Study subjects provided informed consent and signed clinical research informed consent forms.

1.2 Study methods

General information of all subjects was recorded, including age, sex, height, weight, systolic blood pressure,

diastolic blood pressure, etc. Body mass index (BMI) was calculated. After a 10-hour overnight fast, fasting venous blood was collected on the morning of admission. Fasting blood glucose (FBG), glycated hemoglobin (HbA1c), fasting insulin, fasting C-peptide, lipid profile, electrolytes, 25-hydroxy vitamin D [25-(OH)D], creatine kinase (CK), creatine kinase isoenzyme (CK-MB), and lactate dehydrogenase (LDH) were measured on the same day. Homeostatic model assessment for insulin resistance (HOMA-IR) was calculated as fasting insulin × fasting glucose / 22.5. Doppler ultrasound (Philips, models EPIQ 7C and IE33, probe frequency 1-5 MHz) was used to measure left ventricular ejection fraction (LVEF), left ventricular end-diastolic diameter (LVEDD), interventricular septal thickness (IVST), and left ventricular posterior wall thickness (LVPWT).

1.3 Exclusion criteria

(1) Use of exogenous insulin; (2) History of congenital heart disease; (3) History of cardiac-related diseases such as coronary heart disease, valvular heart disease, etc.; (4) Presence of infection; (5) Use of drugs known to affect lactate metabolism such as metformin; (6) Abnormal liver or kidney function, gastrointestinal diseases, malignancies; (7) Mobility impairment, elderly frailty, communication barriers, inability to complete all tests; (8) Family history of hereditary diseases.

1.4 Statistical methods

SPSS 25.0 software was used for statistical analysis. Normally distributed continuous data were presented as $\bar{x}\pm s$ and analyzed using independent sample *t*-tests. Non-normally distributed continuous data were presented as *M (P25, P75)* and analyzed using non-parametric tests. Count data were presented as case and analyzed using chi-square tests. Spearman rank correlation analysis was used to assess the correlation between blood lactate and various indicators. Multiple linear regression analysis was used to assess the linear dependence of blood lactate on various indicators. $P<0.05$ indicated statistical significance.

2 Results

2.1 Comparison of age, sex, BMI, and biochemical indicators between two groups

Compared to the normal lactate group, patients in high lactate group had younger age, higher proportion of males, increased FBG, HbA1c, insulin resistance index, triglycerides (TG), very low-density lipoprotein cholesterol (VLDL-C), and decreased 25-(OH) D ($P<0.05$). **See Table 1.**

2.2 Comparison of cardiac function indicators between two groups

LVEDD was higher and LVEF was lower in T2DM patients with elevated blood lactate compared to those with normal lactate ($P<0.01$). **See Table 2.**

Tab. 1 Comparison of general information and biochemical indexes between two groups

Indicator	Normal lactate group（*n*=88）	High lactate group（*n*=100）	$t/\chi^2/Z$ value	*P* value
Blood lactate (mmol/L)a	2.35±0.69	2.88±0.76	3.276	0.001
Age（years）[a]	65.57±12.20	60.56±14.32	2.564	0.011
Male/female (case)	36/52	64/36	10.020	0.001
BMI（kg/m²）[a]	24.47±3.24	25.03±3.25	1.181	0.239
FBG（mmol/L）[b]	7.36（6.16，9.80）	8.46(7.10,10.84)	2.205	0.027
HbA1c（%）[b]	7.35（6.45，8.71）	8.36(7.27,10.31)	2.598	0.009
Insulin （uU/mL）[b]	6.34（4.65，10.60）	7.41(5.19,12.06)	1.314	0.189
C-peptide （ng/mL）[b]	3.34（2.45，5.00）	3.61(2.48,4.72)	0.572	0.567
HOMA-IR[b]	2.19（1.28，3.89）	2.96（1.79，4.59）	2.082	0.037
25-（OH）D（ng/mL）[a]	18.61±6.64	15.82±6.53	2.335	0.021
TC（mmol/L）[a]	4.12±1.19	4.42±1.24	1.359	0.176
TG（mmol/L）[b]	1.04（0.87,1.52）	1.49（1.07,2.27）	3.075	0.002
HDL-C（mmol/L）[a]	1.28±0.34	1.30±0.35	0.386	0.700
LDL-C（mmol/L）[b]	2.34（1.72,3.17）	2.52（1.99，3.45）	1.312	0.190
VLDL-C（mmol/L）[b]	0.60（0.43,0.82）	0.77（0.55，1.39）	2.865	0.004
Uric acid （μmol/L）[a]	269.59±74.39	293.60±97.03	1.463	0.146
Creatinine （μmol/L）[b]	66.50（58.00，77.75）	60.00 (50.50，72.00)	1.757	0.079

Note：[a] represented as $\bar{x}\pm s$; [b] represented as M（P_{25}, P_{75}）; Body mass index (BMI); High density lipoprotein cholesterol (HDL-C); Low density lipoprotein cholesterol (LDL-C).

Tab.2 Comparison of cardiac function indexes between two groups

Indicator	Normal lactate group（*n*=88）	High lactate group（*n*=100）	*t*/*Z* value	*P* value
LDH（u/L）[a]	174.66±40.58	168.03±38.82	1.144	0.254
CK（u/L）	78.50（52.50,111.25）	63.50(50.25,95.00)	1.119	0.230
CK-MB（u/L）	12.50（9.25,15.75）	11.00(9.00,15.19)	0.895	0.371
LVEF (%)[a]	62.23±5.42	47.07±5.28	19.402	<0.001
LVEDD (mm)[a]	44.16±4.38	54.77±4.07	17.210	<0.001
IVST(mm)[b]	10.50（10.00,12.00）	11.00(10.00,12.00)	0.217	0.828
LVPWT(mm)[b]	10.00（9.00,10.00）	10.00(9.00,11.00)	1.079	0.281
Systolic blood pressure（mmHg）[b]	133.00(126.00,146.00)	134.00（126.25，150.75）	0.421	0.674
Diastolic blood pressure (mmHg)[b]	79.00（75.00，86.00）	80.00(76.00,86.00)	0.478	0.632

Note：[a] represented as $\bar{x}\pm s$; [b] represented as M（P_{25}, P_{75}）.

2.3 Spearman correlation analysis between blood lactate and various indicators

Blood lactate levels were positively correlated with FBG, HbA1c, HOMA-IR, VLDL-C, TG, and LVEDD (*r*=0.204, 0.203, 0.213, 0.282, 0.324, 0.600; *P*<0.05); blood lactate levels were negatively correlated with sex and LVEF (*r*=-0.172, -0.646; P<0.05); there was no correlation between blood lactate levels and age or 25-(OH) D (*r*=-0.131, -0.084; *P*>0.05).

2.4 Multiple linear regression analysis of factors influencing blood lactate

Indicators that showed statistically significant correlation with blood lactate were included in multiple linear regression analysis, and the result showed that LVEF and LVEDD were influencing factors for blood lactate (*P*<0.01). **See Table 3.**

Tab.3 Multiple linear regression analysis affecting blood lactate levels

Factors	β（95%*CI*）	*β'*	*t value*	*P* value
Constant	2.306（0.246，4.366）		2.214	0.028
Female	-0.025（-0.243，0.193）	-0.016	-0.223	0.824
FBG	-0.007（0.246，4.366）	-0.027	0.275	0.784
HbA1c	0.036（-0.030，0.101）	0.098	1.079	0.283
HOMA-IR	0.038（-0.007，0.082）	0.126	1.681	0.095
LVEF	-0.030（-0.046，-0.013）	-0.343	-3.547	0.001
LVEDD	0.033（0.009，0.056）	0.275	2.759	0.007
TG	-0.046（-0.156，0.064）	-0.146	-0.828	0.409
VLDL	0.187（-0.126，0.500）	0.210	1.180	0.240

3 Discussion

This study investigated blood lactate levels in 188 patients with T2DM and found that 69.4% of T2DM patients had elevated blood lactate levels, with males showing higher levels than females. Eljaaly *et al.* [4] reported higher uric acid concentrations in male diabetic patients compared to females, suggesting that gender may influence metabolic functions. Previous studies have indicated a positive association between blood lactate and elevated estradiol, and a negative association between blood lactate and testosterone levels [5]. In contrast, our study's results may be biased due to the selected data, necessitating further research to validate underlying mechanisms. The study found that the age of the high lactate group was slightly younger than the normal lactate group, but Spearman correlation analysis showed no correlation. Similar conclusions were drawn by Xiang *et al.* [6], suggesting lower blood lactate levels in elderly patients compared to younger and middle-aged patients, indicating a negative correlation with age. Although research on blood lactate levels across different age groups is limited, it is speculated that elevated lactate levels are associated with aging and declining metabolic levels, potentially influenced by data biases in this study, requiring further investigation.

Most studies suggest correlations between blood lactate and FBG, HbA1c, and pancreatic function [7]. Elevated blood glucose levels in diabetic patients can impair mitochondrial activity, increase intracellular glycolysis processes, leading to lactate accumulation, ultimately raising blood lactate levels [8]. A prospective study of Japanese T2DM patients showed a positive correlation between blood lactate levels and FBG and HbA1c [2], consistent with our findings: different blood lactate level groups showed differences in FBG, HbA1c, and insulin resistance index, while insulin and C-peptide levels did not significantly differ, suggesting a closer relationship between blood lactate and blood glucose concentrations than pancreatic function.

Clinical studies have demonstrated a negative correlation between circulating 25-(OH)D levels and HbA1c [9]. In this study, the high lactate group had higher HbA1c and lower 25-(OH)D levels compared to the normal group, similar to previous research findings. Vitamin D appears to be a potential regulator of insulin secretion, with active vitamin D participating in insulin biosynthesis and secretion. In a study involving 417 Japanese individuals at risk of diabetes, significant effects of alfacalcidol in preventing T2DM were observed, especially in participants with insufficient insulin secretion [10]. Additionally, vitamin D supplementation can improve insulin secretion [11], reducing diabetes risk by approximately 11%.

Blood lactate is associated with blood lipid parameters. in this study, the high lactate group had higher TG and VLDL levels than the normal lactate group, and Spearman correlation analysis showed a positive

correlation between blood lactate and TG, VLDL. There is a certain correlation between blood lactate and blood lipids. A study injecting lactate into mouse muscles and administering forskolin, an activator of the cAMP-PKA pathway, via intramuscular and intraperitoneal routes, investigated the role of the cAMP-PKA pathway in lactate-induced intramuscular TG accumulation and increased mitochondrial content; after 5 weeks of lactate injection, TG levels increased in mouse gastrocnemius muscles. The study suggested that lactate-induced intramuscular TG accumulation is achieved by inhibiting lipolysis, regulated by the cAMP-PKA pathway [12]. In this study, T2DM patients in the high lactate group had higher blood lipids, and interventions such as diet control and moderate exercise to reduce blood lipids may benefit metabolism and lower blood lactate levels.

The study results also showed that the high lactate group had significantly lower LVEF and higher LVEDD compared to the normal lactate group, with a negative correlation between blood lactate levels and LVEF, and a positive correlation with LVEDD. Multiple linear regression analysis results indicated that LVEF and LVEDD are factors influenced by blood lactate, suggesting a correlation between T2DM patients with elevated blood lactate and impaired cardiac function; the higher the blood lactate, the lower the LVEF and the larger the LVEDD, indicating worse cardiac function and prognosis. Increasing evidence suggests that impaired mitochondrial oxidative phosphorylation is associated with decreased oxidative capacity, which correlates with insulin resistance and T2DM [13]. In T2DM patients, insulin resistance-induced inhibition of insulin signaling can trigger a series of immune reactions, exacerbating inflammatory states [14], potentially further impairing mitochondrial function and affecting oxidative capacity. Elevated blood glucose in T2DM accompanied by high lactate levels results in the formation of advanced glycation end products (AGEs); AGEs are glycosylated proteins or lipids exposed to glucose for prolonged periods. AGEs can crosslink with extracellular matrix proteins, increase fibrosis, impair myocardial relaxation, activate intracellular damage through AGE receptors, increase cytoplasmic reactive oxygen species (ROS), and activate inflammation pathways through NF-κB signaling. ROS can mediate mitochondrial uncoupling, and mitochondrial damage leads to impaired intracellular calcium handling. Sarcoplasmic reticulum calcium transport ATPase (SERCA-2) enters the sarcoplasmic reticulum to reuptake calcium, which is an energy-dependent process. Insufficient energy may lead to abnormal cardiac contraction and relaxation [15], increasing the likelihood of heart failure before and after.

In summary, there is a certain correlation between T2DM accompanied by elevated blood lactate and cardiac dysfunction, but the specific mechanisms require further study. For patients with T2DM, achieving standard blood glucose and lipid levels are important measures to reduce blood lactate levels and maintain cardiac function.

The authors report no conflict of interest

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·论　著·

2 型糖尿病患者血乳酸水平与心功能的相关性分析

乔焱[1]，　李俊[2]，　李青菊[2]

1. 郑州大学，河南 郑州 450000；

2. 郑州大学第二附属医院内分泌科，河南 郑州 450000

摘要：目的　检测 2 型糖尿病(T2DM)患者血乳酸水平,并分析其与心功能各指标的相关性。**方法**　采用横断面研究方法,选取 2023 年 4 月至 7 月于郑州大学第二附属医院内分泌科就诊的 T2DM 患者 188 例为研究对象。根据血乳酸结果是否大于 2.5 mmol/L,将其分为血乳酸升高组(n=100)和血乳酸正常组(n=88)。所有患者于收治次日空腹抽静脉血检测血生化、心肌酶标志物及心脏彩超检测左心室射血分数(LVEF)、左室舒张末期内径(LVEDD)等指标,分析 T2DM 患者血乳酸水平与心功能指标的相关性。**结果**　与血乳酸正常组比较,血乳酸升高组年龄较小,男性比例较高(P<0.05);空腹血糖(FBG)、糖化血红蛋白(HbA1c)、稳态模型评估—胰岛素抵抗(HOMA-IR)指数、三酰甘油(TG)、极低密度脂蛋白胆固醇(VLDL-C)升高(P<0.05),25 羟基维生素 D[25-(OH)D]降低(P<0.05);LVEDD 增高(P<0.01),而 LVEF 降低(P<0.01)。Spearman 相关分析显示,血乳酸水平与 FBG、HbA1c、HOMA-IR、VLDL-C、TG 和 LVEDD 分别成正相关(r=0.204、0.203、0.213、0.282、0.324、0.600,P<0.05);与性别、LVEF 分别成负相关(r=-0.172、-0.646, P<0.05);与年龄、25-(OH)D 无相关性(r=-0.131、-0.084, P>0.05)。多元线性回归分析结果显示,LVEF 和 LVEDD 是血乳酸的影响因素(P<0.05)。**结论**　在 T2DM 患者中,血乳酸水平升高,心功能下降。

关键词： 2 型糖尿病；血乳酸；血糖；心功能不全；稳态模型评估—胰岛素抵抗指数

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Correlation between blood lactate level and cardiac function in patients with type 2 diabetes mellitus

QIAO Yan*, LI Jun, LI Qingju

Zhengzhou University, Zhengzhou, Henan 450000, China

Corresponding author: LI Qingju, E-mail: liqingju1133@163.com

Abstract: Objective　To detect the blood lactate levels in patients with type 2 diabetes mellitus (T2DM) and analyze its correlation with various cardiac function indexes. **Methods**　A cross-sectional study was conducted on 188 T2DM patients treated in the Department of Endocrinology, The Second Affiliated Hospital of Zhengzhou University from April to July 2023. Based on whether the blood lactate level was greater than 2.5 mmol/L, they were divided into elevated blood lactate group (n=100) and normal blood lactate group (n=88). On the next day of admission, all enrolled patients underwent fasting venous blood tests for biochemical analysis and myocardial enzyme markers. Echocardiography was used to measure left ventricular ejection fraction (LVEF), left ventricular end-diastolic diameter (LVEDD), and other indexes. The correlations between blood lactate levels and cardiac function indexes in patients with T2DM were analyzed. **Results**　Compared with the normal blood lactate group, the patients in the elevated blood lactate group were younger, and had a higher proportion of males (P<0.05); Fasting blood glucose (FBG), glycated hemoglobin (HbA1c), Homeostasis model assessment of insulin resistance index (HOMA-IR), triacylglycerol (TG), very low density lipoprotein cholesterol (VLDL-C) increased (P<0.05), and 25 hydroxyvitamin D [25-(OH) D] decreased (P<0.05); LVEDD increased (P<0.01), while LVEF decreased (P<0.01). Spearman correlation analysis showed that

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通信作者： 李青菊，E-mail: liqingju1133@163.com

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blood lactate level was positively correlated with FBG, HbA1c, HOMA-IR, VLDL-C, TG, and LVEDD (r = 0.204, 0.203, 0.213, 0.282, 0.324, 0.600, P<0.05), respectively; and negatively correlated with gender and LVEF (r = −0.172, −0.646, P<0.05), respectively; but not with age or 25-(OH) D (r = −0.131, −0.084, P>0.05). Multiple linear regression analysis showed that LVEF and LVEDD were influencing factors of blood lactate (P < 0.05). **Conclusion** In patients with T2DM, blood lactate increase and cardiac function decrease.

Keywords: Type 2 diabetes mellitus; Blood lactate; Blood glucose; Cardiac dysfunction; Homeostasis model assessment of insulin resistance index

Fund program: Joint Co-construction Project of Henan Medical Science and Technology Research Plan (LHGJ20220453)

最新数据显示 2 型糖尿病(T2DM)在糖尿病人群中占 90%以上[1]。血浆乳酸浓度与糖酵解速率相关,而糖酵解速率的关键在于线粒体氧化能力[2]。在 T2DM 患者中,持续存在的高血糖状态会促进炎性因子的释放,导致机体长期处于慢性亚临床炎症状态。这种状态可能会对线粒体功能产生损害,从而影响糖酵解速率,并增加乳酸堆积的风险[3]。骨骼肌和心肌是产生乳酸的主要组织。当心脏功能不全时,心脏泵血受阻,可能导致循环血容量不足,进而引发组织缺氧。这种情况下,糖酵解速率减慢,导致组织器官中乳酸生成增加而代谢减少,造成乳酸堆积,进而可出现高乳酸酸血症,甚至可能引发乳酸酸中毒。尽管现在已有研究表明乳酸与 T2DM 之间的关系,但 T2DM 患者乳酸水平和心功能不全的相关性研究有限。本研究分析 T2DM 患者血乳酸水平及影响因素,并评估其与心功能不全的相关性。

1　对象与方法

1.1　*研究对象*　采用横断面研究,选取 2023 年 4 月至 7 月于郑州大学第二附属医院就诊的 T2DM 患者 188 例。所有患者均进行了血乳酸测定,根据血乳酸结果是否大于 2.5 mmol/L,将其分为血乳酸升高组(n=100)和血乳酸正常组(n=88)。本研究经郑州大学第二附属医院伦理委员会批准(批件号 2023081),研究对象均签署知情同意书。

1.2　*研究方法*　记录所有研究对象一般资料。每位受试者隔夜禁食 10 h,于收治次日早晨抽取静脉全血。当日内采用全自动生化仪进行空腹血糖(FBG)、糖化血红蛋白(HbA1c)、空腹胰岛素、空腹 C 肽、血脂、电解质、25 羟基维生素 D[25-(OH)D]、肌酸激酶(CK)、肌酸激酶同工酶(CK-MB)、乳酸脱氢酶(LDH)测定。稳态模型评估-胰岛素抵抗(HOMA-IR)指数=空腹胰岛素×空腹血糖/22.5。采用彩色多普勒超声诊断仪(生产企业:飞利浦;型号:EPIQ 7C、IE33,1~5MHz 的探头频率)测量左室射血分数(LVEF)、左室舒张末期内径(LVEDD)、室间隔厚度(IVST)、左室后壁厚度(LVPWT)。

1.3　*排除标准*　(1)应用外源胰岛素;(2)有先心病史;(3)有心脏病史,如冠心病、心脏瓣膜病等;(4)合并感染;(5)应用二甲双胍等已知影响乳酸代谢的药物;(6)肝肾功能异常,消化道疾病,恶性肿瘤;(7)行动不便、交流障碍、不能配合完成所有检查者;(8)有家族病史、遗传病史。

1.4　*统计学方法*　应用 SPSS 25.0 软件进行数据分析。符合正态分布的计量资料以 $\bar{x}\pm s$ 表示,采用独立样本 t 检验;不符合正态分布的计量资料以 $M(P_{25}, P_{75})$ 表示,采用非参数检验。计数资料以例表示,采用 χ^2 检验。相关分析应用 Spearman 秩相关。用多元线性回归分析血乳酸与各指标的线性依存关系。P<0.05 为差异有统计学意义。

2　结　果

2.1　*两组一般资料及生化指标*　血乳酸升高组年龄小于血乳酸正常组;男性比例高于乳酸正常组(P<0.05);男性血乳酸水平高于女性[(2.92±0.82) mmol/L *vs* (2.65±0.69) mmol/L, t = 2.296, P = 0.023];FBG、HbA1c、HOMA-IR、三酰甘油(TG)、极低密度脂蛋白胆固醇(VLDL-C)高于血乳酸正常组(P<0.05),25-(OH)D 低于血乳酸正常组(P<0.05)。见表 1。

2.2　*两组心功能指标比较*　血乳酸升高组患者的 LVEDD 高于血乳酸正常组(P<0.01),LVEF 低于血乳酸正常组(P<0.01)。见表 2。

2.3　*血乳酸与各指标 Spearman 相关分析*　血乳酸水平与 FBG、HbA1c、HOMA-IR、VLDL-C、TG 和 LVEDD 成正相关(r = 0.204、0.203、0.213、0.282、0.324、0.600, P<0.05);与性别、LVEF 成负相关(r = −0.172、−0.646, P<0.05);与年龄、25-(OH)D 无相关性(r = −0.131、−0.084, P>0.05)。

2.4　*影响血乳酸水平的多元线性回归分析*　将与血

乳酸有统计学意义相关性的指标纳入多元线性回归分析,结果显示,LVEF 和 LVEDD 是血乳酸水平的影响因素(P<0.01)。见表 3。

表 1　两组一般资料及生化指标比较

Tab. 1　Comparison of general information and biochemical indexes between two groups

项目	血乳酸正常组(n=88)	血乳酸升高组(n=100)	$t/\chi^2/Z$ 值	P 值
血乳酸(mmol/L)[a]	2.35±0.69	2.88±0.76	3.276	0.001
年龄(岁)[a]	65.57±12.20	60.56±14.32	2.564	0.011
性别(男/女,例)	36/52	64/36	10.020	0.001
BMI(kg/m^2)[a]	24.47±3.24	25.03±3.25	1.181	0.239
FBG(mmol/L)[b]	7.36(6.16, 9.80)	8.46(7.10, 10.84)	2.205	0.027
HbA1c(%)[b]	7.35(6.45, 8.71)	8.36(7.27, 10.31)	2.598	0.009
胰岛素(μU/mL)[b]	6.34(4.65, 10.60)	7.41(5.19, 12.06)	1.314	0.189
C 肽(ng/mL)[b]	3.34(2.45, 5.00)	3.61(2.48, 4.72)	0.572	0.567
HOMA-IR[b]	2.19(1.28, 3.89)	2.96(1.79, 4.59)	2.082	0.037
25-(OH)D(ng/mL)[a]	18.61±6.64	15.82±6.53	2.335	0.021
总胆固醇(mmol/L)[a]	4.12±1.19	4.42±1.24	1.359	0.176
TG(mmol/L)[b]	1.04(0.87, 1.52)	1.49(1.07, 2.27)	3.075	0.002
HDL-C(mmol/L)[a]	1.28±0.34	1.30±0.35	0.386	0.700
LDL-C(mmol/L)[b]	2.34(1.72, 3.17)	2.52(1.99, 3.45)	1.312	0.190
VLDL-C(mmol/L)[b]	0.60(0.43, 0.82)	0.77(0.55, 1.39)	2.865	0.004
尿酸(μmol/L)[a]	269.59±74.39	293.60±97.03	1.463	0.146
肌酐(μmol/L)[b]	66.50(58.00, 77.75)	60.00 (50.50, 72.00)	1.757	0.079

注:[a] 以 $\bar{x}\pm s$ 表示;[b] 以 $M(P_{25}, P_{75})$ 表示;BMI(身体质量指数);HDL-C(高密度脂蛋白胆固醇);LDL-C(低密度脂蛋白胆固醇)。

表 2　两组心功能指标比较

Tab. 2　Comparison of cardiac function indexes between two groups

项目	血乳酸正常组(n=88)	血乳酸升高组(n=100)	t/Z 值	P 值
LDH(u/L)[a]	174.66±40.58	168.03±38.82	1.144	0.254
CK(u/L)	78.50(52.50, 111.25)	63.50(50.25, 95.00)	1.119	0.230
CK-MB(u/L)	12.50(9.25, 15.75)	11.00(9.00, 15.19)	0.895	0.371
LVEF (%)[a]	62.23±5.42	47.07±5.28	19.402	<0.001
LVEDD (mm)[a]	44.16±4.38	54.77±4.07	17.210	<0.001
IVST(mm)[b]	10.50(10.00, 12.00)	11.00(10.00, 12.00)	0.217	0.828
LVPWT(mm)[b]	10.00(9.00, 10.00)	10.00(9.00, 11.00)	1.079	0.281
收缩压(mmHg)[b]	133.00(126.00, 146.00)	134.00(126.25, 150.75)	0.421	0.674
舒张压(mmHg)[b]	79.00(75.00, 86.00)	80.00(76.00, 86.00)	0.478	0.632

注:[a] 以 $\bar{x}\pm s$ 表示;[b] 以 $M(P_{25}, P_{75})$ 表示。

表 3　血乳酸水平影响因素的多元线性回归分析

Tab. 3　Multiple linear regression analysis of influencing factors of blood lactate levels

相关因素	偏回归系数(95%CI)	标准误	标准回归系数	t 值	P 值
常量	2.306(0.246, 4.366)	0.420		2.214	0.028
性别[a]	−0.025(−0.243, 0.193)	0.044	−0.016	−0.223	0.824
FBG[b]	−0.007(0.246, 4.366)	0.010	−0.027	0.275	0.784
HbA1c (%)	0.036(−0.030, 0.101)	0.013	0.098	1.079	0.283
HOMA-IR	0.038(−0.007, 0.082)	0.009	0.126	1.681	0.095
LVEF(%)	−0.030(−0.046, −0.013)	0.003	−0.343	−3.547	0.001
LVEDD(mm)	0.033(0.009, 0.056)	0.005	0.275	2.759	0.007
TG[b]	−0.046(−0.156, 0.064)	0.022	−0.146	−0.828	0.409
VLDL-C[b]	0.187(−0.126, 0.500)	0.064	0.210	1.180	0.240

注:[a] 表示以男性为参照;[b] 表示单位为 mmol/L。

3　讨　论

本研究在 188 例 T2DM 患者中发现 69.4%血乳酸水平上升,且男性血乳酸水平较女性高。Eljaaly 等[4]研究显示糖尿病患者中的男性血尿酸浓度高于女性,表明性别可能对体内代谢功能产生影响。既往有研究指出血乳酸随雌二醇水平升高而增加,随睾酮水平升高而降低[5],本研究结果与之相反,可能与本研究数据选择有偏倚相关。本研究发现乳酸升高组年龄较正常组稍小,但 Spearman 相关分析显示无相关性,向玉平等[6]研究曾得出类似结论:与青年和中年患者相比,老年患者的血乳酸水平较低,表明年龄与血乳酸浓度之间存在一定的负相关性。推测高血乳酸水平可能与年龄增长、代谢水平下降相关,也可能是由于本文数据选择存在潜在偏倚,以后需要进一步研究验证。

大多数研究认为血乳酸与 FBG、HbA1c 以及胰岛功能之间均存在相关性[7],糖尿病患者的血糖浓度升高会造成线粒体活性受损,进而增加细胞内的糖酵解过程,导致乳酸堆积,最终引起血乳酸水平的升高[8]。日本一项 T2DM 患者的前瞻性研究显示,血乳酸水平与 FBG 和 HbA1c 呈正相关[2],本研究结果与之相符:不同血乳酸水平组患者的 FBG、HbA1c 和 HOMA-IR 差异有统计学意义,而胰岛素、C 肽水平无显著差异,表明血乳酸与血糖浓度之间的关系更为密切,而与胰岛功能关系较小。

临床研究已经证明,循环中的 25-(OH)D 水平与 HbA1c 呈负相关[9],在本研究中,血乳酸升高组 HbA1c 较血乳酸正常组高,而 25-(OH)D 较血乳酸正常组低,与既往研究结论相似。维生素 D 似乎是胰岛素分泌的潜在调节因子,活性维生素 D 参与胰岛素的生物合成和分泌。在日本一项涵盖 417 例糖尿病前期个体的研究中,特别是在胰岛素分泌不足的参与者中,可以观察到艾地骨化醇在预防 T2DM 方面的显著效果[10]。此外,补充维生素 D 也可以改善胰岛素的分泌[11],使糖尿病风险降低 11%左右。

血乳酸与血脂参数有关,本研究血乳酸升高组 TG、VLDL 高于血乳酸正常组,Spearman 相关分析显示血乳酸与 TG、VLDL 呈正相关。血乳酸和血脂之间存在一定的相关性。在一项实验中通过向小鼠肌内注射乳酸和腹腔注射环磷酸腺苷-蛋白激酶 A(cAMP-PKA)途径激活剂 Forsklin 的方法,研究 cAMP-PKA 途径在乳酸诱导的肌内 TG 蓄积和线粒体含量增加中的作用;注射乳酸 5 周后,小鼠腓肠肌

内 TG 水平升高,提示乳酸诱导的肌内 TG 蓄积是通过抑制脂肪分解实现的,这一过程受 cAMP-PKA 途径的调控[12]。本研究 T2DM 患者血乳酸升高组血脂较高,通过控制饮食、适量运动等干预措施降低血脂,可能对改善代谢和降低血乳酸有一定的益处。

本研究结果还显示,血乳酸水平与 LVEF 成负相关,与 LVEDD 成正相关。多元线性回归分析结果显示,LVEF、LVEDD 是血乳酸的影响因素,表明血乳酸越高,LVEF 越低、LVEDD 越大,此时 T2DM 患者心功能越差,预后越差。越来越多的证据表明,线粒体氧化磷酸化功能受损与氧化能力的下降相关,而这种下降与胰岛素抵抗和 T2DM 存在关联[13]。在 T2DM 患者中,胰岛素抵抗引起的胰岛素信号传导抑制会导致一系列免疫反应,从而加重炎症状态[14],这可能进一步损害线粒体功能,影响氧化能力。T2DM 伴血乳酸升高组中空腹血糖及 HbA1c 均较正常组高,血乳酸升高与 T2DM 的发生发展及加重可形成恶性循环。高血糖导致晚期糖基化终产物(AGEs)形成,AGEs 可与细胞外基质蛋白交联,增加纤维化,损害心肌舒张,AGEs 也可通过激活 AGEs 受体引起细胞内损伤,导致胞质活性氧(ROS)增加,并通过 NF-κB 信号激活炎症途径,ROS 可介导线粒体解耦,线粒体损伤导致细胞内钙处理受损。肌溶酶体内质网钙转运 ATP 酶通过进入肌浆网来进行钙再摄取,这是一个依赖能量的过程。如果能量不足,可能会导致心肌收缩和舒张功能异常[15],增加心脏前后负荷,从而增加心功能不全发生的可能性。

综上所述,T2DM 伴血乳酸升高与心功能不全存在一定的相关性,但具体的机制还需要进一步研究。对于 T2DM 患者,控制血糖、血脂达标,都是降低血乳酸水平和维护心功能的重要措施。

作者贡献　乔焱提出主要研究目标,负责研究的构思、设计与实施,以及论文撰写;李俊进行论文的修订;李青菊负责文章的质量控制与审查,对文章整体负责,并监督管理。

利益冲突　无

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