



# Serum Levels of Carbamylated LDL, Nitrotyrosine and Soluble Lectin-like Oxidized Low-density Lipoprotein Receptor-1 in Poorly Controlled Type 2 Diabetes Mellitus

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**Introduction:** Carbamylated low-density lipoprotein (cLDL) has profound proatherogenic properties. Lectin-like oxidized low-density lipoprotein receptor-1 (LOX-1) has been identified as the primary cLDL receptor. The soluble form of LOX-1 (sLOX-1) and 3-nitrotyrosine (NT) have recently been suggested as biomarkers of vascular disease. Although type 2 diabetes mellitus (T2DM) is characterised by an increased atherosclerotic risk, the clinical data on cLDL, NT and sLOX-1 levels in T2DM are limited.

**Aim:** To explore the possible role of cLDL, NT and sLOX-1 as potential biomarkers for disease progression and complications in poorly controlled T2DM patients with and without microalbuminuria.

**Materials and methods:** The serum concentrations of cLDL, NT and sLOX-1 were measured by ELISA in a cross-sectional study of 60 T2DM patients and 35 nondiabetic controls.

**Results:** Both the normoalbuminuric (n = 34) and the microalbuminuric (n = 26) patients had significantly higher serum levels of cLDL and NT than the healthy controls, but sLOX-1 was only elevated in the microalbuminuric subgroup ( $p < 0.05$ ). Carbamylated LDL correlated positively with NT in the diabetic subjects ( $r_s = 0.266$ ,  $p = 0.04$ ) while it correlated with urea only in the control group ( $r_s = 0.475$ ,  $p = 0.004$ ). The serum concentration of sLOX-1 correlated significantly with fasting glucose ( $r_s = 0.441$ ,  $p < 0.001$ ), HbA1c ( $r_s = 0.328$ ,  $p = 0.01$ ) and microalbuminuria ( $r_s = 0.272$ ,  $p = 0.035$ ) in the whole diabetic cohort.

**Conclusions:** The present study highlights the potential of cLDL, NT and sLOX-1 as possible markers of diabetic complications.

## Key words:

carbamylated LDL, sLOX-1, nitrotyrosine, diabetes mellitus, microalbuminuria

## INTRODUCTION

Diabetes mellitus (DM) is characterised by an elevated risk for development of atherosclerosis which is closely related to diabetic microvascular and macrovascular com-

plications. Atherosclerosis is a complex multifactorial disease but many lines of evidence indicate that endothelial cell injury by modified low-density lipoprotein (LDL) is a critical early event in atherogenesis. In the pathologic conditions of DM circulating and intrainitmal LDLs are sub-

jected to multiple enzymatic and nonenzymatic chemical modifications.<sup>1</sup> Whereas oxidized LDL (oxLDL) has been extensively explored, there are only a few investigations of carbamylated LDL (cLDL).<sup>2</sup> Carbamylation of LDL is a result of the spontaneous nonenzymatic binding of isocyanate to the N-terminal protein amine groups or to multiple lysine residues of apolipoprotein B.<sup>3</sup> Isocyanate is the active form of urea-derived cyanate which is normally present in low concentrations in plasma and significantly increased in renal failure.<sup>3</sup> Therefore, the pathological impact of carbamylation has been predominantly investigated in patients with end-stage renal disease (ESRD) and on hemodialysis. Apostolov et al. have recently reported that cLDL is the most common LDL isoform not only in uremic patients but also in healthy individuals.<sup>4</sup> Subsequently, Wang et al. have revealed an alternative urea-independent pathway for carbamylation mediated by myeloperoxidase (MPO).<sup>5</sup> MPO is a heme containing enzyme abundant in the granules of neutrophils, monocytes and certain tissue macrophages such as those found in human atheroma. At inflammatory sites and in atherosclerotic plaques MPO catalyses the oxidation of thiocyanate in the presence of hydrogen peroxide, thus producing isocyanate.<sup>5</sup> Another posttranslational protein modification catalysed by MPO and accelerated in atherosclerosis is the nitration of the aromatic amino acid tyrosine, generating 3-nitrotyrosine (NT). Nitrotyrosine can also be formed through peroxynitrite-mediated pathway and has been delineated as a stable marker for assessment of oxidative stress.<sup>6</sup>

Carbamylated LDL has been shown to possess all the major atherosclerotic activities, including binding to macrophage scavenger receptors (SRs), promoting cholesterol accumulation and foam cell formation.<sup>2</sup> Carbamylated LDL causes endothelial cell apoptosis<sup>7</sup> as well as accelerated senescence in human endothelial progenitor cells.<sup>8</sup> Furthermore, cLDL stimulates expression of cell adhesion molecules<sup>9,10</sup> and proliferation of vascular smooth muscle cells (VSMCs).<sup>9</sup>

These adverse biological effects of cLDL are mediated by a number of SRs but lectin-like oxidized low-density lipoprotein receptor-1 (LOX-1) has been recognised as the primary cLDL receptor.<sup>10</sup> LOX-1 is a class E scavenger receptor, first identified as the major SR for oxLDL in endothelial cells (ECs).<sup>11</sup> It is also expressed by other cell types highly involved in atherogenesis such as macrophages and VSMCs.<sup>12</sup> A soluble form of LOX-1 (sLOX-1) has recently been identified as a product of proteolytical cleavage of LOX-1 membrane proximal extracellular domain. It has been demonstrated that sLOX-1 may reflect expression of membrane-bound LOX-1 and serum sLOX-1 levels are elevated in patients with acute coronary syndrome.<sup>13</sup> Type 2 DM (T2DM) has been suggested as a condition that increases LOX-1 expression, since diabetes harvests all the major inducers of LOX-1 expression including oxLDL, shear stress, proinflammatory cytokines and angiotensin II.<sup>12</sup> In addition, in vitro, animal and human studies have indicated that LOX-1 expression is increased by hypergly-

cemia and advanced glycation end products (AGEs).<sup>14-16</sup> In contrast, only in vitro studies have demonstrated that LOX-1 can be upregulated by cLDL.<sup>10</sup>

## AIM

The aim of the current study was to explore the possible role of cLDL, NT and sLOX-1 as potential biomarkers for disease progression and complications in poorly controlled T2DM patients with and without microalbuminuria. Therefore, the serum concentrations of cLDL, NT and sLOX-1, the relationships between them and the associations with routine biochemical parameters were analysed.

## MATERIALS AND METHODS

**Subjects:** The study included 60 patients with poorly controlled T2DM [i.e. glycated hemoglobin (HbA1c)  $\geq 7\%$ ], diagnosed according to the American Diabetes Association criteria.<sup>17</sup> Diabetic patients were defined as having normoalbuminuria (<30 mg/24 h) and microalbuminuria (30–300 mg/24 h) according to their urinary albumin excretion rate.<sup>17</sup> The control group comprised of 35 healthy sex- and age-matched subjects who had no history of DM or impaired glucose tolerance, hypertension and obesity. All the participants in the cross-sectional study met the following inclusion criteria: no acute or chronic infections or inflammatory disease, no active immunological disease, no advanced cardiovascular diseases (CVD) and renal impairment, no other known chronic illness, pregnancy and alcohol abuse. Patients on lipid lowering agents were excluded. Smokers were also not recruited in the study since smoking has been shown to augment both carbamylation<sup>5</sup> and tyrosine nitration.<sup>6</sup>

The study was approved by the Human Ethics Committee of Medical University of Plovdiv (No 4/21.09.2017) and was conducted in accordance with the Declaration of Helsinki. All participants signed an informed consent.

**Laboratory analysis:** Clinical data, fasting blood and urinary samples were collected. Plasma fasting glucose (FG), total cholesterol (TC) and triglycerides (TG) were determined enzymatically using a Beckman Coulter AU480 analyzer (Beckman Instruments Inc., USA). HDL-cholesterol was measured using a direct method with polyethylene glycol-modified enzymes and alpha-cyclodextrin. LDL-cholesterol was calculated using the Friedewald's equation: [LDL-cholesterol] = [TC] - [HDL-cholesterol] - ([TG]/2.2) where all concentrations are given in mmol/l.<sup>18</sup> The level of HbA1c was analysed in whole blood by immunoturbidimetric inhibition method. Plasma urea was measured by kinetic urease/glutamate dehydrogenase method and creatinine by the Jaffe method. Urinary albumin excretion was measured by turbidimetric method.

Serum concentrations of cLDL and sLOX-1 were determined using commercially available ELISA kits (MyBio-

Source Inc., San Diego, CA, USA). Commercial ELISA kits were also used for quantification of serum levels of hsCRP (BioVendor – Laboratornimedica, Brno, Czech Republic) and protein-bound NT (Hycult Biotech, Uden, the Netherlands). All the tests were performed according to the manufacturer's instructions.

#### STATISTICAL ANALYSIS

Statistical analysis was performed using SPSS software, version 17.0 (SPSS Inc., Chicago, IL, USA). The Kolmogorov-Smirnov test was used to evaluate whether the distribution of continuous variables was normal. Continuous variables were expressed as mean  $\pm$  SD or as median and interquartile range. Analysis of normally distributed variables included an independent-samples t-test and one-way analysis of variance (ANOVA). The Mann-Whitney U and Kruskal-Wallis tests were used for variables with a non-normal distribution. Categorical variables were analysed by a Chi-square test. To address the relationship between variables, Spearman's correlations were performed. The level of significance was set at  $p < 0.05$ .

## RESULTS

The clinical characteristics and metabolic parameters of the study participants are summarized in **Table 1**. Diabetic patients had higher BMI, waist circumference (WC), systolic and diastolic blood pressure (BP) in comparison to controls. As expected in a diabetic population, FG, TC and TG levels were elevated. There was no difference in the levels of urea and HDL-cholesterol among the three groups, while LDL-cholesterol was increased only in the normoalbuminuric patients compared to controls. The two diabetic subgroups did not differ according to HbA1c levels but the microalbuminuric subgroup had higher FG concentration and longer duration of diabetes. The serum levels of cLDL, NT and hsCRP were significantly elevated in both diabetic subgroups compared to controls, whereas no significant difference was found between the diabetics with and without microalbuminuria (**Table 1**). The differences in cLDL and NT remained significant ( $p < 0.05$ ) after adjusting for BMI, levels of LDL-cholesterol, TC, TG, FG and hsCRP. In contrast, there was no significant difference ( $p > 0.05$ ) in sLOX-1 levels between the whole diabetic group [255.7 (137.6–525.8) pg/ml,  $n = 60$ ] and the controls (**Table 1**). However, when divided according to the presence of microalbuminuria, the microalbuminuric patients had significantly higher serum sLOX-1 concentration than their normoalbuminuric and nondiabetic counterparts (**Table 1**).

Diabetic subjects receiving angiotensin-converting enzyme inhibitor (ACEI) or angiotensin II receptor blocker (ARB) had significantly lower serum sLOX-1 levels [201.4 (137.6–315.5) pg/ml,  $n = 26$ ] than those without the particular treatment [349.0 (143.3–594.2) pg/ml,  $n = 34$ ,  $p = 0.044$ ].

Correlation analysis was further performed in the whole

patient and control groups. Surprisingly, cLDL correlated weakly but significantly only with NT in the diabetic subjects (**Table 2**) while it correlated moderately with urea in controls ( $r_s = 0.475$ ,  $p = 0.004$ ,  $n = 35$ ). The duration of diabetes was found to correlate moderately with the level of microalbuminuria ( $r_s = 0.443$ ,  $p < 0.001$ ,  $n = 60$ ), whereas only weakly with NT concentration (**Table 2**). The serum level of sLOX-1 correlated moderately with FG and HbA1c, while weakly but significantly with microalbuminuria within the diabetic cohort (**Table 2**).

In the control group, no correlation was observed between the serum concentration of sLOX-1 and any other metabolic parameter.

## DISCUSSION

Protein carbamylation has previously been considered quantitatively significant only in the continuum of renal diseases as uremia provides a favourable chemical environment for this posttranslational modification.<sup>2,3</sup> Several studies have suggested that carbamylation, and cLDL in particular, are of crucial importance for the higher prevalence of CVD among patients with chronic kidney diseases (CKD).<sup>3,4,7,19</sup> However, the discovery of the urea-independent carbamylation mechanism<sup>5</sup> implies that cLDL should be explored beyond the context of CKD. T2DM is a prominent risk factor for the development of both renal and cardiovascular complications and microalbuminuria is considered as a prognostic marker of these adverse diabetic consequences.<sup>20</sup> Therefore, it seemed reasonable to compare serum cLDL concentrations in T2DM patients with and without microalbuminuria. The current study demonstrated that the diabetic subjects had elevated cLDL levels independently of the presence of microalbuminuria. Carbamylated LDL correlated significantly with urea only in the healthy controls, but not in the diabetic patients. These observations may indicate that cLDL is generated mainly via the nonenzymatic urea-dependent pathway under normal physiological conditions, whereas via the alternative MPO-mediated mechanism in T2DM. Furthermore, augmented MPO levels have been associated with obesity, chronic low-grade inflammation, insulin resistance and T2DM<sup>21</sup> and most of our diabetic participants were overweight or obese (i.e. BMI  $>25.0$ )<sup>17</sup> (**Table 1**).

Another consequence of the enhanced MPO activity is the increased nitration of the amino acid tyrosine.<sup>6</sup> In addition, elevated plasma tyrosine levels have been documented in insulin resistant states.<sup>22</sup> Although there is a discrepancy about systemic NT levels in T2DM,<sup>23</sup> we measured significantly higher serum NT concentrations in the diabetic subjects which even correlated with the disease duration. This is in accordance with the general concept of the key role of oxidative stress in T2DM pathogenesis and progression.<sup>1,23</sup> Moreover, the current study established a positive correlation between the serum levels of cLDL and NT only in the diabetic group. This finding supports the hypothesis

**Table 1.** Clinical characteristics and serum concentrations of cLDL, NT and sLOX-1 in controls and diabetic patients with and without microalbuminuria

Characteristics	Controls (n = 35)	T2DM (n = 60)		p-value
		Normo-albuminuria (n = 34)	Micro-albuminuria (n = 26)	
Sex, Male/Female (no.)	19/16	16/18	15/11	NS <sup>#</sup>
Age (years)	41±11	46±10	44±9	NS
Duration of T2DM (years)	-	4 (2 – 9)	10 (6 – 12)	0.026
Body mass index (kg/m <sup>2</sup> )	22.8±3.0	30.1±4.8 <sup>c</sup>	30.6±2.9 <sup>c</sup>	<0.001
Waist circumference (cm)	83±10	101±9 <sup>c</sup>	105±8 <sup>c</sup>	<0.001
Hypertension (%)	-	50	58	NS <sup>#</sup>
ACEI or ARB (%)	-	41	46	NS <sup>#</sup>
Systolic BP (mmHg)	115±7	130±9 <sup>c</sup>	129±7 <sup>c</sup>	<0.001
Diastolic BP (mmHg)	76±4	80±4 <sup>c</sup>	80±6 <sup>b</sup>	<0.001
Fasting glucose (mmol/l)	4.63±0.47	6.55±1.25 <sup>c</sup>	7.80±1.26 <sup>c,f</sup>	<0.001
HbA1c (%)	Not assessed	9.2 (8.8 – 9.4)	9.2 (9.0 – 9.4)	NS
Total cholesterol (mmol/l)	4.05±0.95	5.17±1.32 <sup>c</sup>	4.87±1.09 <sup>a</sup>	<0.001
Triglycerides (mmol/l)	0.95 (0.75 – 1.35)	1.55 (1.16 – 2.26) <sup>a</sup>	1.61 (1.41 – 1.99) <sup>b</sup>	<0.001
HDL-cholesterol (mmol/l)	1.15 (1.04 – 1.20)	1.20 (1.10 – 1.26)	1.16 (0.97 – 1.46)	NS
LDL-cholesterol (mmol/l)	2.42±0.85	3.13±1.27 <sup>a</sup>	2.94±1.08	0.014
Urea (mmol/l)	5.00±1.24	5.39±1.30	5.47 ±1.54	NS
hsCRP (µg/ml)	0.59 (0.28 – 0.96)	2.98 (2.11 – 4.05) <sup>c</sup>	2.71 (2.00 – 3.79) <sup>c</sup>	<0.001
cLDL (mg/l)	218.4 (175.3 – 313.4)	430.9 (354.6 – 547.4) <sup>c</sup>	402.5 (287.8 – 520.8) <sup>b</sup>	<0.001
NT (nmol/l)	4.67 (1.90 – 18.82)	19.50 (12.18 – 35.07) <sup>c</sup>	20.95 (8.68 – 33.36) <sup>b</sup>	<0.001
sLOX-1(pg/ml)	198.6 (121.1 – 328.6)	201.4 (131.5 – 351.6)	353.9 (206.0 – 728.6) <sup>a,d</sup>	0.029

Data are presented as mean±SD or median (25<sup>th</sup>-75<sup>th</sup> percentile). Differences among the three groups were determined using ANOVA or Kruskal-Wallis tests followed by independent-samples t- and Mann-Whitney U-tests with Bonferroni corrections for multiple comparisons.

<sup>a</sup> p < 0.05 vs controls; <sup>b</sup> p < 0.01 vs controls; <sup>c</sup> p < 0.001 vs controls.

<sup>d</sup> p < 0.05 vs normoalbuminuric patients; <sup>f</sup> < 0.001 vs normoalbuminuric patients.

<sup>#</sup> p-value of Chi-square test.

ACEI: angiotensin-converting enzyme inhibitor; ARB: angiotensin II receptor blocker

**Table 2.** Statistically significant correlations between the study parameters in patients with T2DM (n = 60)

Parameters	$r_s$	p-value
cLDL / NT	0.266	0.04
NT / Duration of diabetes	0.256	0.049
sLOX-1 / Fasting glucose	0.441	<0.001
sLOX-1 / HbA1c	0.328	0.01
sLOX-1 / Microalbuminuria	0.272	0.035

$r_s$ : Spearman's correlation coefficient.

for the MPO-mediated higher concentrations of cLDL in T2DM. It is also in line with the sole investigation of cLDL in T2DM, conducted by Shiu et al.<sup>24</sup>

Initiation of the other, peroxy-nitrite-dependent, NT generation pathway by cLDL may also explain the higher NT levels found in the diabetic patients. Speer et al. demonstrated that binding of cLDL to LOX-1 in ECs led to p38 mitogen-activated protein kinase (MAPK) and NADPH-oxidase activation.<sup>25</sup> Carbamylated LDL also stimulated endothelial nitric oxide (NO) synthase (NOS) uncoupling via S-glutathionylation. Overall, this resulted in increased generation of reactive oxygen species which can react with NO, yielding peroxy-nitrite and subsequently increasing protein tyrosine nitration and decreasing NO availability. Moreover, diminished NO availability and augmented levels of both carbamylation and nitration of plasma proteins have been associated with increased prevalence of CVD.<sup>5,6,22</sup> The observed positive correlation between the significantly higher cLDL and NT levels in the diabetic cohort may be evidence of a crosstalk between these protein posttranslational modifications in T2DM.

In addition, Choi et al. demonstrated that cLDL induced tyrosine nitration of insulin receptor (IR) substrate (IRS) 1 via the upregulation of inducible NOS dependent pathway.<sup>26</sup> It has been documented that tyrosine nitration of IR- $\beta$ , IRS-1, IRS-2, Akt and other signaling molecules from insulin transduction pathway has a deleterious effect on insulin tolerance in skeletal muscles.<sup>27</sup> Moreover, cLDL has been shown to attenuate significantly glucose uptake by decreasing glucose transporter 4 (GLUT4) expression in the membrane, while increasing it in the cytosol of rat L6 skeletal muscle cells.<sup>26</sup> The peripheral insulin resistance is considered to be the initiating or primary event in the pathogenesis of T2DM. Regardless of the presence of microalbuminuria, our diabetic patients had almost two-fold higher levels of cLDL and more than four-fold higher levels of NT in comparison to controls (**Table 1**). Taken together, these data suggest that elevated cLDL and NT as well as the crosstalk between them in T2DM may be involved not only in development of the diabetic complications, but also in the pathogenesis of the disease itself.

LOX-1 has been implicated in vascular inflammation

and atherosclerotic plaque formation and vulnerability.<sup>12,13</sup> Although vascular complications are unambiguously linked to DM and the hyperglycemic milieu has been shown to induce LOX-1 expression,<sup>14,15</sup> the clinical data about sLOX-1 in T2DM are scanty and controversial. Tan et al. demonstrated for the first time that diabetics had higher sLOX-1 concentrations which were positively associated with serum glucose, AGEs and glycemic control.<sup>16</sup> Our study confirmed only partially these results because sLOX-1 significantly correlated with both glucose and HbA1c in the diabetic group. However, we did not register a significant difference in sLOX-1 levels between the whole diabetic and the control groups, as reported by other authors.<sup>13,28</sup> Only the diabetic patients with microalbuminuria showed a significant increase of sLOX-1 level compared both to the control and normoalbuminuric subjects, which is in contrast to a previous investigation.<sup>29</sup> Furthermore, a significant correlation was established between the levels of sLOX-1 and microalbuminuria in the whole diabetic cohort. Poor glycemic control and microalbuminuria are associated with disease progression and adverse cardiovascular and renal consequences.<sup>20</sup> Hence, our results indicate that determination of sLOX-1 concentration might help in prediction of an increased risk of diabetic complications.

Carbamylated LDL has been shown to induce LOX-1 expression in ECs<sup>10</sup> but there is no evidence confirming this effect in vivo. Based on data reporting correlations between serum concentration of sLOX-1 and some of its ligands in diabetes,<sup>15,16,29</sup> we postulated an association between circulating sLOX-1 and cLDL in T2DM. However, our study did not establish such a correlation which could be influenced by the therapy of the diabetic patients. Multiple drugs have been demonstrated to inhibit vascular LOX-1 expression and activity, delineating LOX-1 as an attractive therapeutic target for the prevention and management of atherosclerosis-related diseases.<sup>31</sup> We measured a significantly lower sLOX-1 concentration in diabetics receiving ACEI and ARB which may be a result of the inhibition of the well-established inducing effect of angiotensin II on LOX-1 expression.<sup>12</sup> However, further investigation of pharmacological modulation of LDL carbamylation, LOX-1 expression and cLDL-LOX-1 axis is warranted.

## CONCLUSION

The serum concentration of cLDL is elevated in patients with poorly controlled T2DM, independently of the level of urea or the presence of microalbuminuria, but in association with oxidative stress. The positive correlation between cLDL and NT might imply that carbamylation of LDL is mediated mainly by MPO in T2DM. Our results demonstrate that circulating sLOX-1 correlates with glycemic control and microalbuminuria, but not with cLDL. Microalbuminuria, poor glycemic control and increased levels of cLDL and NT have been associated with adverse cardiovascular and renal consequences. Therefore, the present study

underscores the potential of cLDL, NT and sLOX-1 as possible markers of diabetic complications.

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## Сывороточные уровни карбамелированных липопротеинов низкой плотности, нитротирозина и растворимого лектиноподобного окисленного рецептора-1 липопротеина низкой плотности при плохо контролируемом сахарном диабете 2 типа

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**Введение:** Карбамелированный липопротеин низкой плотности (cLDL) обладает сильными проатерогенными свойствами. Лектиноподобный окисленный рецептор-1 липопротеина низкой плотности (LOX-1) был идентифицирован в качестве первичного рецептора cLDL. Растворимая форма LOX-1 (sLOX-1) и 3-нитротирозина (НТ) в последнее время считаются биомаркерами сосудистых заболеваний. Хотя сахарный диабет 2 типа (СДТ2) характеризуется повышенным риском развития атеросклероза, клинические данные об уровнях cLDL, НТ и sLOX-1 при СДТ2 ограничены.

**Цель:** Исследовать вероятную роль cLDL, НТ и sLOX-1 в качестве потенциальных биомаркеров для развития заболевания и осложнений у пациентов с плохо контролируемым СДТ2 с и без микроальбуминурии.

**Материалы и методы:** Сывороточные концентрации cLDL, НТ и sLOX-1 были измерены методом ELISA в перекрестном исследовании 60 пациентов с СДТ2 и 35 пациентов без диабета в качестве контрольной группы.

**Результаты:** У пациентов с нормальной альбуминурией (n = 34) и у пациентов с микроальбуминурией (n = 26) были значительно более высокие сывороточные уровни cLDL и НТ по сравнению со здоровыми пациентами из контрольной группы, но sLOX-1 был повышен только в подгруппе микроальбуминурии (p < 0,05). Карбамелированные ЛПНП положительно коррелировали с НТ у пациентов с диабетом ( $r_s = 0,266$ , p = 0,04), а в то же время коррелировали с мочевиной только в контрольной группе ( $r_s = 0,475$ , p = 0,004). Концентрация sLOX-1 в сыворотке значительно коррелировала с уровнем глюкозы натощак ( $r_s = 0,441$ , p < 0,001), HbA1c ( $r_s = 0,328$ , p = 0,01) и микроальбуминурией ( $r_s = 0,272$ , p = 0,035) во всей группе диабетиков.

**Выводы:** Настоящее исследование подчеркивает потенциал cLDL, НТ и sLOX-1 в качестве вероятных маркеров осложнений диабета.