



Research article

Lipid peroxidation processes in men with type 1 diabetes mellitus following α -lipoic acid treatment

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Abstract: In various pathological conditions such as diabetes mellitus, the cellular redox balance can be disturbed and these alterations may persist even after blood glucose levels have returned to normal. Antioxidant therapies, including α -lipoic acid, are widely used to treat various systemic diseases including diabetes mellitus. The aim of this study was to measure the lipid metabolism parameters, as well as the activity of lipid peroxidation and antioxidant defense reactions, in men with type 1 diabetes mellitus (T1DM) during treatment with α -lipoic acid. Twenty-four reproductive-age T1DM males with an unsatisfactory glycemic profile were examined. Twenty-eight practically healthy men of similar age were used as the control group. Spectrophotometric, fluorometric, and enzyme-linked immunoassay methods were used. T1DM was characterized by increased values of lipid metabolism components, including total cholesterol, triacylglycerides (TG), and very-low-density lipoproteins (VLDL). In the lipid peroxidation system, increased levels of the primary products (conjugated dienes), secondary products (thiobarbituric acid reactants), and final products (Schiff bases) were observed in T1DM patients compared to the control group. Retinol values were also increased. After treatment, there was a decrease in TG, VLDL, and Schiff bases levels and an increase in the retinol level compared to before treatment. These results expand our understanding of the pathogenetic mechanisms of T1DM and suggest that α -LA treatment may be beneficial for type 1 diabetics.

Keywords: type 1 diabetes mellitus; lipid peroxidation; antioxidants; α -lipoic acid

Abbreviations: AOD: Antioxidant defense; BMI: Body mass index; CDs: Conjugated dienes; DM: Diabetes mellitus; DNA: Deoxyribonucleic acid; HbA1c: Glycosylated hemoglobin; HDL: High-density lipoproteins; GPO: Glutathione peroxidase; LDL: Low-density lipoproteins; LPO: Lipid

peroxidation; OS: Oxidative stress; ROS: Reactive oxygen species; SOD: Superoxide dismutase; T1DM: Type 1 diabetes mellitus; TBARs: Thiobarbituric acid reactants; TC: Total cholesterol; TG: Triacylglycerides; SB: Schiff bases; VLDL: Very-low-density lipoproteins; WHO: World health organization; α -LA: α -lipoic acid

1. Introduction

Diabetes mellitus (DM) is a group of metabolic diseases characterized by chronic hyperglycemia, which is the result of impaired insulin secretion or action, or both these factors [1]. Data from the International Diabetes Association indicate that approximately 483 million people of the global adult population suffer from DM and, according to forecasts, this figure may almost double by 2035 [2]. The Russian Federation is among the leading countries in DM but the true prevalence of DM is approximately 3–4 times higher than the official data (9–10 million people) [3]. The number of patients with type 1 diabetes mellitus (T1DM) in the RF population is more than 250000 people [4].

Reactive oxygen species (ROS) are chemically active, oxygen-containing molecules that are natural by-products of oxygen metabolism in all aerobic organisms [5]. Mitochondria are the main suppliers of ROS, but there are also alternative mechanisms that contribute to their formation, including NADPH-oxidase, immune reactions, xanthine oxidase, and arachidonic acid metabolism [6]. ROS are involved in the processes of intracellular signaling, through which the cellular activity is regulated, including apoptosis induction, adaptation to the effects of various factors, and the immune response [7]. Increased accumulation of ROS leads to oxidative stress (OS), which damages the main cellular components, including lipids, proteins, and DNA [8]. Damage to the lipid components leads to the development of lipid peroxidation (LPO) reactions. The antioxidant defense (AOD) system limits the damaging effects of ROS. During various pathological conditions, including DM, the cellular redox balance can be disturbed [9]. The interaction of ROS with cellular components ultimately leads to their modification and these changes can persist even after the normalization of blood glucose levels [10,11]. This phenomenon is the basis of the so-called “metabolic memory” mechanism, which is based on the products of OS reactions [12].

Modern antioxidant therapy—for example, treatment with α -lipoic acid (α -LA), α -tocopherol, vitamin C, or selenium—is widely used for several systemic diseases including DM [11,13]. α -Lipoic acid is part of the AOD system and is an effective free-radical scavenger, as well as a cofactor for a number of metabolic reactions [14].

The development of diabetes in young people, in particular, in the male population, increases the importance of the prevention and treatment of the complications of DM due to the high risk of reproductive health disorders. The aim of this study was to determine the lipid metabolism parameters, as well as the activity of lipid peroxidation and antioxidant defense reactions, in males with T1DM during α -lipoic acid treatment.

2. Materials and methods

2.1. Design of study

Fifty-two patients of the Irkutsk Regional Clinical Hospital endocrinology department (Russia) were included in the study. Twenty-four reproductive-age men (average age 29.4 ± 9.8 years old) with

T1DM with an unsatisfactory glycemic profile were examined. Data from 28 practically healthy men of similar age (average age 29.7 ± 4.6 years old) were used as the control group. Inclusion criteria in the group of patients with T1DM included: male; age 18–40 years old; informed consent of the patient to participate in the study; resident in the Irkutsk region; verified diagnosis of T1DM. Exclusion criteria: type 2 or other type of DM; presence of severe complications of DM (proteinuria, renal failure, macrovascular complications); presence of other endocrine diseases; presence of pronounced concomitant somatic pathology. Inclusion criteria in the control group: male; age 18–40 years old; normal indicators of glucose tolerance; no hereditary predisposition to DM. Exclusion criteria in the control group: presence of acute or exacerbation of chronic diseases at the time of the examination. Comprehensive medical examinations of patients with T1DM were carried out according to the DM classification (WHO, 1999), DM diagnostic criteria (WHO, 1999–2018), and algorithms of specialized medical care for patients with DM. All patients were on basic bolus insulin therapy using analogs of human insulins of long and ultrashort action. The regimens and doses for each patient were selected individually. For antioxidant treatment, α -lipoic acid (Solution Acid Thioctici 600.0 + Solution NaCl 200.0 intravenously for 10 days) was used.

2.2. Ethics approval

All participants signed an informed consent form to participate in the study in accordance with the World Medical Association Declaration of Helsinki (1964, 2013 ed.). The study was approved by the Biomedical Ethics Committee at the Scientific Centre for Family Health and Human Reproduction Problems, Russia, together with Irkutsk Regional Clinical Hospital (No. 8.2, dated November 2, 2018).

2.3. Biochemical measurements

The parameters of lipid metabolism and the products of LPO-AOD were measured in serum, plasma, and hemolysate. Blood was taken for analysis from the ulnar vein taking into account the generally accepted requirements.

Blood plasma was obtained by centrifugation at 3000 g for 5 min at 4 °C. Samples were stored at 80 °C until analysis. Dynamic monitoring of patients throughout the entire period of their stay in the hospital was carried out.

The level of glycosylated hemoglobin (HbA1c) was determined using a D-10 analyzer (Bio-Rad, USA) using liquid ion-exchange high-performance chromatography. Capillary blood glucose was determined using the glucose oxidase method. The glycemic profile (fasting blood glucose and postprandial glucose level 2 hours after eating) was analyzed.

The levels of total cholesterol (TC), high-density lipoproteins (HDL), and triglycerides (TG) in serum were determined using commercially available kits (BioSystems, Spain) and a Synchron SH9 Pro biochemical analyzer (Beckman Coulter, USA). The content of low-density lipoproteins (LDL) was calculated using the following formula: $LDL = TC - (HDL + VLDL)$, where the level of very-low-density lipoproteins ($VLDL = TG/2.2$).

The method for measuring the primary LPO products content in blood plasma is based on the absorption at 232 nm of the conjugated diene (CD) structures of lipid hydroperoxides [15]. The coefficient of molar absorption ($K = 2.2 \times 10^5 \text{ M}^{-1} \text{ C}^{-1}$) was used to convert absorption units to $\mu\text{mol/L}$. Plasma TBARs levels were determined using a thiobarbituric acid reaction followed by measurement

of the fluorescence intensity at 515 nm (excitation) and 554 nm (emission) [16]. TBARs concentration is expressed in $\mu\text{mol/L}$. Plasma Schiff bases (SB) levels were determined by fluorescence [17]. Blood plasma α -tocopherol and retinol levels were detected [18].

The activity of superoxide dismutase (SOD) and glutathione peroxidase (GPO) was determined in hemolysate using commercial kits from Randox (UK) and a Shimadzu (Japan) RF-1501 spectrofluorophotometer and RF-1650 spectrophotometer. Enzyme immunoassays were read on a MultiSkan ELX808 microplate reader (Biotek, USA).

This work was carried out using the equipment of the Centre of Collective Usage “Center for the Development of Progressive Personalized Health Technologies”, Scientific Centre for Family Health and Human Reproduction Problems, Irkutsk.

2.4. Statistical procedure

The results were analyzed with STATISTICA 10.0 software (StatSoft Inc., USA). Data are presented as M —mean, σ —standard deviation. To determine the proximity to the normal distribution law of quantitative features, we used the visual-graphical method and the Kolmogorov–Smirnov agreement criterion with Lilliefors and Shapiro–Wilk correction. Due to the abnormal data distribution, differences in the quantitative indicators between the study groups were assessed using the Mann–Whitney U-test. Spearman’s correlation analysis was used to analyze intra-group relationships of quantitative traits. The significance level was assumed to be $p < 0.05$.

3. Results

The basic characteristics of the patients are demonstrated in Table 1. The analysis of the main characteristics in men with T1DM showed a statistically significant decrease in the level of the average daily glucose in patients with T1DM after α -LA treatment compared with the data before treatment ($p < 0.0001$; Table 1).

Table 1. Clinical characteristics of the men with T1DM ($M \pm \sigma$).

Indicators	Control	Patients
Age, years	29.71 ± 4.59	29.38 ± 9.78
DM duration, years	-	8.36 ± 4.45
HbA _{1c} , %	-	10.36 ± 1.99
BMI	21.5 ± 1.12	22.42 ± 2.85
Average daily glucose		
Before α -LA treatment (mmol/l)	-	10.56 ± 2.88
After α -LA treatment (mmol/l)	-	$7.91 \pm 1.06^*$

*Note: Statistically significant difference compared to the group before treatment. DM: Diabetes mellitus; HbA_{1c}: Glycosylated hemoglobin; BMI: Body mass index.

In the analysis of the lipid metabolism state in men with T1DM before α -LA treatment, values of TC were increased by 1.13 times ($p = 0.005$), TG by 1.69 times ($p = 0.007$), and VLDL by 1.71 times

($p = 0.007$) relative to the healthy control group (Figure 1). After treatment, the α -LA-treated patients still showed increased TG values (1.41 times; $p = 0.043$) relative to the control. However, compared with the data before treatment, there was a decrease in the TG level (1.2 times; $p = 0.038$) and VLDL (1.5 times; $p = 0.039$; Figure 1).

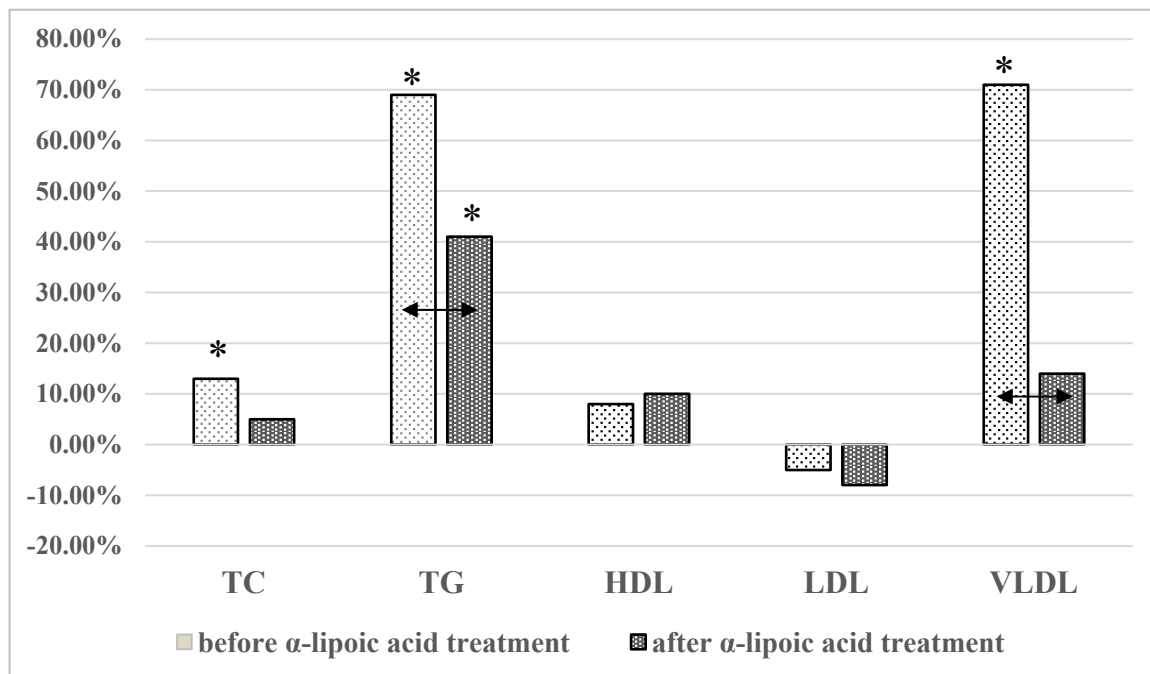


Figure 1. Changes in the levels of serum lipids in men with T1DM; * statistically significant difference compared with the control group (the values of the control group are taken as 0%); ↔ — statistically significant differences between groups.

In men with T1DM, compared to before α -LA treatment (Figure 2), the level of CDs was significantly increased by 2.27 times ($p < 0.0001$), TBARs by 1.56 times ($p < 0.0001$), and SB by 1.95 times ($p = 0.002$). In the antioxidant defense system in men with T1DM, the retinol values were increased by 1.37 times ($p = 0.003$) compared to the control group.

After α -LA treatment, the T1DM group still showed increased value relative to the control (Figure 2): CDs by 2.04 times ($p < 0.0001$), TBARs by 1.44 times ($p < 0.001$), and SB by 1.76 times ($p < 0.0001$). The SB level was decreased by 1.11 times ($p = 0.041$) and the retinol level increased (1.18 times; $p = 0.039$) relative to the data before treatment. The activity of the antioxidant enzyme GPO (1.33 times; $p = 0.018$) and the retinol level (1.63 times; $p < 0.0001$) increased relative to the control values (Figure 2).

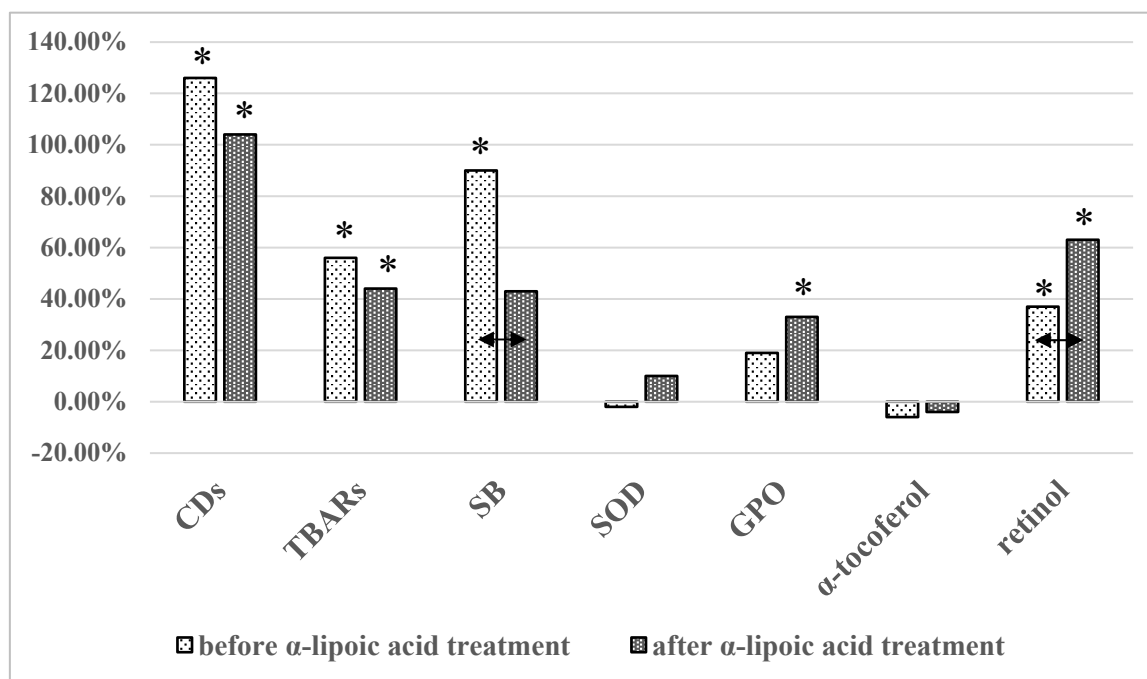


Figure 2. Changes in the parameters of the LPO–AOD system in men with T1DM before and after α -lipoic acid treatment; * statistically significant difference compared with the control group (the values of the control group are taken as 0%); ↔ — statistically significant differences between groups.

4. Discussion

Our analysis of the lipid metabolism parameters in men with T1DM before α -LA treatment showed elevated values of a number of components of the LPO–AOD system, including total cholesterol, triacylglycerides, and very-low-density lipoproteins. Dyslipidemia is a distinct and serious factor in the progression of diabetic complications due to the direct relationship between complex lipid disorders and microvascular disorders [19–21]. However, in patients with T1DM, lipid metabolism disorders are, as a rule, more rare and less pronounced. With adequate control of glycemia, this category of patients is characterized by a reduced level of TG and LDL [22]. In addition, insulin therapy can contribute to an increase in the level of HDL, which is caused by the stimulation of lipoprotein lipase activity in adipose tissue and skeletal muscles and, accordingly, VLDL intensive metabolism [19]. The severity of dyslipoproteinemia in T1DM increases with the development of diabetic complications [23–25].

The changes in the contents of LPO products in men with T1DM indicate the presence of pro-oxidant activity at all stages of the process. Oxidative stress is a unifying factor of the main pathways involved in the development and progression of diabetic complications [26]. In excess amounts, LPO products are highly toxic and have a damaging effect on the structural components of the cell such as lipoproteins, proteins, enzymes, and nucleic acids [27]. Thus, lipid hydroperoxides may inhibit DNA synthesis, induce apoptotic processes, suppress cell proliferation, maturation, and growth, and cause mutational changes [28]. Further LPO products include aldehydes and ketones that are involved in the synthesis of prostaglandins and a number of steroids. As a result of the interaction between dialdehydes

and free groups of membrane compounds, the final LPO products (Schiff bases) are formed, the accumulation of which destabilizes the membranes and promotes cell destruction [7,11]. An increase in toxic LPO products indicates the involvement of LPO processes in the pathogenetic mechanisms of developing structural and functional disorders [29–31]. Here, we observed an increase in toxic SB products consistent with previous studies indicating an increase in the LPO products in disease [32,33].

These changes occur when the AOD system is not able to neutralize the toxic effect of ROS. In our study, there were no differences in the level of SOD, GPO, or α -tocopherol in patients relative to the control. However, there was an increase in the values of retinol. Retinol is a strong antioxidant that protects membranes from damage by, for example, superoxide and peroxide radicals [11]. An increase in the retinol concentration may be a compensatory mechanism aimed at neutralizing toxic LPO products. However, due to the increase in LPO products at all stages, there is likely a significant shift towards pro-oxidant processes in the redox balance in men with T1DM.

α -Lipoic acid treatment of patients with T1DM led to a relative stabilization of the studied parameters. We noted a less pronounced increase in the values of LPO products relative to the control, a decrease in the level of TG and VLDL, as well as a decrease in the content of SB, and an increase in the level of retinol in the group of T1DM patients compared to the data before treatment. There was also a significant decrease in the average daily glucose concentration in the blood of patients with T1DM during treatment.

The high redox potential of α -LA means that it can neutralize most LPO products, hydroxyl radicals, and singlet oxygen in both oxidized and reduced forms [14]. Furthermore, as it has both hydrophilic and hydrophobic sites in its structure, α -LA shows activity in both the cytosol and blood serum and in biological membranes [34]. Another important property of α -LA is the ability to regenerate other endogenous antioxidants, in particular vitamins E and C [35]. Our study showed an increase in retinol values in the α -LA treatment group. Probably, these changes can be associated with a possible synergistic effect of vitamin E. The α -LA molecule contains a dithiolan ring in an oxidized form, the presence of which provides the formation of dihydrolipoic acid, which, like ascorbic acid, promotes the transformation of vitamin E into a reduced form. The reduced form of α -LA is a potent reducing agent for regenerating oxidized antioxidants such as ascorbate, glutathione, coenzyme Q10, and vitamin E. Under these conditions, an increase in retinol concentration seems likely. Under natural conditions, α -LA is contained in the mitochondria of cells, where it is bound to the E2 subunit and acts as a coenzyme for pyruvate dehydrogenase and α -ketoglutarate dehydrogenase [36]. α -LA is synthesized in the body *de novo* from fatty acids and cysteine in small amounts, therefore, exogenous sources of α -LA are important. Exogenous administration, α -LA has a pronounced anti-inflammatory, hypoglycemic, and antioxidant effect [14]. Furthermore, α -LA reduces the ROS level and thus promotes the restoration of endothelial function and reduces blood pressure [37]. Therefore, the decrease in the final LPO products detected in response to treatment with α -LA may be due to the multifunctional nature of the antioxidant. It was previously reported that the administration of α -LA at doses of 300–1200 mg/day for three to six months had a positive effect on various markers of OS, such as malondialdehyde, SOD, GPO, prostaglandin 2 α -isoprostane, and 8-hydroxy-2'-deoxyguanosine [38]. The increase in retinol values seen in this study may be due to the ability of α -LA to regenerate the reduced forms of other antioxidants, such as vitamins.

Due to an increase in β -oxidation of fatty acids and an increase in energy consumption, α -LA affects lipid metabolism and reduces lipogenesis [36] and, after treatment with α -LA, an increase in HDL occurs [14]. The changes in the parameters of lipid metabolism in men with T1DM after

treatment may be due to the direct participation of α -LA in the modulation of certain pathways of lipid synthesis and oxidation, as well as cholesterol utilization through the liver. There is also evidence that α -LA has a pronounced hypoglycemic effect since it improves the absorption and use of glucose by fat cells and skeletal muscles [14,38]. It is likely that the decrease in blood glucose levels in patients with T1DM may be due to these functions of α -LA.

5. Conclusions

The results of the study conducted in men with T1DM and an unsatisfactory glycemic profile indicate an increase in atherogenic lipid fractions and the activation of pro-oxidant processes along with a compensatory increase in retinol levels. The α -LA treatment contributed to a relative normalization of different indicators including a decrease in the levels of the final products of LPO and an increase in retinol. It is necessary to control these indicators in patients with T1DM to prevent complications.

Conflict of interest

All authors declare no conflicts of interest in this paper.

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